THE CHICAGO MEDICAL SCHOOL
QUARTERLY

VOLUME 12, NUMBER 1 OCTOBER, 1950

CONTENTS

•

ORIGINAL ARTICLES

•

FEATURES

THE CHICAGO MEDICAL SCHOOL
QUARTERLY
VOLUME 12 OCTOBER, 1950 NUMBER 1

ARTERIAL HYPERTENSION — ITS NATURE AND TREATMENT *

IRVINE H. PAGE, M.D.**

Introduction

We are now becoming aware that the incidence of hypertension increases as the life span is prolonged. The seriousness of the situation has only been recognized in the past few years and even this recognition is limited to a well informed few among the medical profession and the laity. The term "hypertensive vascular disease" is broad and inclusive, and means a state in which arterial tension is increased over long periods of time and one which is usually associated with premature damage to blood vessels and to the tissues and organs they supply. It has no etiologic and often little physiologic connotation.

Any reasoned study leads at once to the conclusion that arterial hypertension is not a specific disease process but that a variety of different abnormal causes and mechanisms can increase systolic and diastolic arterial pressures. We find it convenient to classify cases of hypertension into two major groups. The first includes those in whom the underlying abnormality is either known or surmised. Unfortunately, the second includes the majority of patients, in whom the nature of the process is not understood and whose disease is therefore termed "essential hypertension".

Classification

Hypertension of known origin can be sub-classified as (1) of central nervous origin, as perhaps in porphyria; (2) of cardiovascular origin, as in arteriosclerosis of large vessels and coarctation of the aorta; (3) of endocrine origin, as in adrenal pheochromocytoma or in Cushing's syndrome; (4) of renal origin as in glomerulonephritis and pyelonephritis.

Attempts have been made to read into hypertension of unknown origin an etiologic classification which follows somewhat similar lines. This is obviously unjustified. But we do find value in estimating in every patient the separate contributions of the nervous, cardiovascular, endocrine and renal systems to the clinical picture, even if we do not accept any of these as of primary etiologic significance. Insofar as a contribution can be assessed and its activity alleviated, the hypertensive process will be relieved. A specific syndrome can be separated out from essential hypertension, the "hypertensive diencephalic syndrome", in which the neurogenic contribution is unmistakable. The estimation of other factors is more difficult since it demands a searching evaluation of the patient as a whole. Such an examination may uncover latent primary genetic factors such as unsuspected pyelonephritis, pheochromocytoma or arteritis, adrenal tumor or cortical hyperplasia. The examination must include more than a casual history taking, a cursory physical, routine urinalysis, electrocardiogram and a quick look at the fundi.

Essential hypertension is characterized by persistent elevation of systolic and diastolic arterial pressures. In its earliest stages the elevations of arterial pressure

* Abstrated from the first annual Maurice Oppenheim Memorial Lecture of Alpha Rho Chapter of the Phi Lambda Kappa Fraternity delivered at Mt. Sinai Hospital of Chicago on May 5, 1950.

** Director of Research, Cleveland Clinic Foundation, Cleveland, Ohio.

are transitory and subside promptly on rest. In its later stages arterial pressure elevations are more severe, more lasting, more resistant to minor modes of treatment. Finally the levels of pressure tend to stabilize at high levels. At any stage in the disease, but more commonly during the phases of persistent elevation of pressure, there appear evidences of advancing arteriolar sclerosis which are reflected in damage to the brain and in lesser degree to the retina, kidney, and other vascular beds. With these go signs of damage to the function of the myocardium.

The hypertension of aortic arteriosclerosis is of particular significance in considering the treatment in hypertensive vascular disease. The increase in arterial pressure is largely systolic. It is due to a failure of the aorta, which has become inelastic, to expand and adapt its capacity to the blood ejected from the heart during each beat. Consequently, there is an abrupt rise in systolic tension in the large arteries as blood is forced into them on its way to the arterioles. The extent to which systolic pressure rises depends upon cardiac rate and output and most of all on stroke volume. Consequently, anything which tends to change stroke volume or cardiac output tends to have a parallel effect on systolic tension. Thus it is not paradoxical, but entirely logical that this form of hypertension, in which the large arteries are least elastic, is also the form in which the levels of systolic tension fluctuate most widely. Cardiac output in intact human beings is predominantly under nervous control, but varies also with metabolic rate, tissue demands and other factors. Therefore it is a common experience that mild measures such as rest, sedation, and control of obesity, which tend to decrease cardiac output, often have dramatic results in decreasing arterial pressure in elderly people.

Arteriosclerotic hypertension, in contrast to essential hypertension, is a disease which begins in middle and old age. Usually in the fifties transient increases in systolic tension occur, which, as time goes on, become persistent. The diastolic pressure is little if at all increased. The underlying disease is a general arteriosclerosis. But this disease has a very slow rate of progress. Although vascular accidents can occur without warning, most of these people live to very nearly a normal expectancy of life. The treatment of this condition is basically the treatment of old age and of vascular complications as they appear.

Pathogenesis

The basic mechanism of arterial hypertension lies in arteriolar vasoconstriction associated with a sensitively and accurately associated increase in cardiac effort. The heart of the patient labors unduly and tires prematurely but it is the load and not the output which has increased. The peripheral vessels are constricted, but, thanks to the delicate balance of cardiac effort and peripheral resistance, the blood flow to most tissues is not abnormally decreased. In the early stage of the process, before it has become overladen with the blood vessel destroying consequence of high pressure and strain, blood flow to the brain and kidney are normal, which together account for about 40% of the total blood flow to the body. Since the kidney is the first organ to show excessive arteriolar constriction and extensive vascular damage in hypertension, the methodology of the measurement of renal hemodynamics provide reliable indices to the advance of hypertensive arteriolar disease.

Essential hypertension is thus characterized as a state of persistent increase of systolic and diastolic arterial pressure with normal cardiac output and with widespread vasoconstriction. In its earlier phases the tissues peripherally are normally perfused. Later the adequacy of the perfusion decreases because of hypertensive arteriolar disease. Quite in accord with pathological findings the first tissue to demonstrate inadequate perfusion is the kidney. As such, essential hypertension differs remarkably from arteriosclerotic hypertension, in which the hypertension is largely systolic and the mechanical abnormality is a loss of elasticity in the large elastic arteries, principally the aorta.

The malignant phase of essential hyper-

tension is a rapidly progressive form of the disease which may complicate a more benign essential hypertension or which may appear as a bolt from the blue. Not infrequently, the syndrome of malignant hypertension complicates one of the hypertensions of known origin. It is characterized by hemorrhagic necrosis of arterioles most widespread in the kidneys. The chronic process is reflected in the fundi of hemorrhages, exudates and papilledema. In the kidney, there results hematuria, proteinuria and rapid loss of excretory function. As a result, in contrast to the less severe forms of hypertension where death is usually due to diseases of the heart or brain, in malignant hypertension, death is almost always due to uremia. Prognosis is most unfavorable.

In considering the causes of hypertension, the greatest contributions of the past 20 years lie in the experimental production of hypertension and hypertensive arterial disease in animals by provoking abnormalities of renal, neurogenic and endocrine functions. Renal hypertension is produced by any means which alters in some specific way the flow of blood through the kidney, viz., by partial compression of the renal artery, or of the aorta above the renal artery, or by the establishment of a diffuse collagenous perinephritis. This may be due to the participation of the renal pressor system. Briefly, this system consists of an enzyme, renin, contained in the tubular cells, which acts on renin substrate, an alpha$_2$-globulin produced by liver to produce a third substance, angiotonin. It is clinically important to recognize that such renal hypertension as this is independent of renal excretory function even in its severe or malignant form, although there also seems to be another type of renal hypertension which depends on suppression of renal excretory function. Clinically the two forms probably blend. Neurogenic hypertension is produced by resection of buffer nerves to the carotid sinus and aorta. Unfortunately, this experimental disease differs in important details from clinical essential hypertension. Attempts to establish a closer neurogenic analogue by direct intervention on higher nervous centers have not as yet been reproducibly successful. In the endocrine panel, Selye's production of hypertension in rats by administration of desoxycorticosterone and high sodium diets suggests a mechanism for hypertension and nephrosclerosis in Cushing's syndrome. Those hypertensive patients who respond to low sodium diets may be those in whose disease an adrenal cortical disturbance plays an important part.

Treatment

1. *General Measures.*

The principles of these general measures can be summed up as follows: (1) cultivating serenity; (2) living a life of moderation; (3) coming to terms with the inevitable; (4) participating only in those affairs which one can influence; (5) avoiding fatigue; (6) having more frequent periods of rest; (7) avoiding obesity; (8) avoiding food fads and eating a well balanced diet in small repasts; (9) selecting a physician in whom the patient can place full responsibility for wise council.

Excessive nervousness contributes greatly towards keeping the blood pressure elevated. Its control is often a complex problem. If, as often happens, it is associated with the female menopause, administration of stilbesterol (0.1-0.5 mg) daily with meals may do much to alleviate it. Occasionally it is due to marked hyperthyroidism when it should be treated as any other case of this disease. Phenobarbital (30 mg. t.i.d.) is a useful sedative and may be continued for a long time if necessary. Psychiatric care has its place in the treatment of some patients. If hypertension occurs in association with one of those rare diseases such as tumor of the adrenal gland, clearly the treatment consists in removing the exciting cause.

2. *Nephrectomy.*

If it is shown that disease is limited to only one kidney, its removal has been observed in a few cases to be followed by the return of the blood pressure to near normal levels. The indications for nephrectomy are unfortunately not so simple. There is no known method which dem-

onstrates that one kidney is entirely normal and the other diseased. Reduced excretory function in one kidney is no criterion of disease. Actually, there is no direct relationship between excretory efficiency and height of the blood pressure. Nor is there any clearly defined relation between hypertension and the appearance of the kidney, as demonstrated by the pyelogram. Secondly, it has been shown in rats that when the blood pressure has been elevated for months or years, removal of the offending kidney is not followed by a return to normal. Much the same seems true in humans.

Thus if it is shown by x-ray examination or by kidney function tests that one kidney is obviously infected and that hypertension has developed in the past two or three years, and that the other kidney seems normal, it is probably desirable to remove the affected kidney. Here the indications are urological rather than medical. But if the hypertension has persisted for five years or more, if there are evidences of arteriolar sclerosis, or if the evidence of unilateral disease is uncertain, it would appear better to avoid the operation. In doubtful cases, a clearly positive family history of hypertension may be a contraindication since familial hypertension is more often "essential" than renal. In general, it is wise to view nephrectomy as a procedure which should be done when removal of the kidney would be desirable on urological grounds. Only occasionally, a patient is seen, in whom abolition of the hypertension is the prime object of the operation.

3. *Potassium Thiocyanate.*

There are two schools of thought about this salt's value. Many are convinced that it has a real place in the treatment of hypertensives. It lowers arterial blood pressure moderately in roughly 40% of the patients and has a mild sedative effect if optimal levels of thiocyanate are reached in the blood stream. It often is a most valuable remedy for intractable headaches that afflict hypertensives. These appear to be its most special virtues.

Its drawbacks consist chiefly of the fact that it often causes a feeling of intense lassitude. Eruptions on the skin and mucous membranes may occur. In older patients mental disturbances have occasionally been encountered. It has been not uncommon to see patients who were said to respond unfavorably to thiocyanate, but who, when carefully controlled, showed no toxic signs and even a favorable response.

4. *Sympathectomy.*

Dorso-lumbar and splanchnic nerve resection as methods of treating patients with hypertension, just as thiocyanate, have been greeted with cheers or jeers. Fortunately, sympathectomy for the treatment of hypertension developed empirically and before hypotheses were advanced to explain it. In fact, if it had depended on some of them, it might never have been practiced. Thus, it has been suggested that the effect of the operation does not depend on denervation of the vasomotor apparatus of the abdomen other than the kidneys but rather on the relief of ischemia. In this view renal denervation alone should be fully effective, whereas it has no effect. Further, the view depends on renal ischemia as the cause of hypertension, whereas such ischemia is not necessarily present either in experimental hypertension or in hypertension in human beings. Lastly, the operation only rarely increases renal blood flow, which is usually unchanged after an otherwise satisfactory operation. The fact that renal blood flow does not usually decrease after sympathectomy when arterial pressure has fallen, indicates that renal resistance must have diminished and, although without reference to the hypothesis of renal ischemia, it has also been suggested that this fact establishes a beneficial and specific effect of renal denervation. This point of view, too, is defective in that it ignores the normal autonomy of the renal circulation by which the kidney varies its resistance with arterial pressure in order to maintain as well as can be a normal rate of blood flow. There is no reason to suppose that this mechanism is in any way defective in hypertensives. Indeed, there is good evidence from the renal hemodynamic effects of

high spinal anesthesia to establish its presence and within limits, normal operation. The persistence of this intrinsic renal mechanism of regulation of blood flow after operation can scarcely be attributed to denervation. Sympathectomy only leaves the kidney where it was before and its effectiveness in lowering arterial pressure is largely extrarenal.

There is now no doubt that when these operations are sufficiently extensive that marked falls in both systolic and diastolic pressures occur in some patients. This is most pronounced when the patient stands erect. Indeed, postural hypotension is one of the best indices of the completeness of the operation. The length of time blood pressure remains reduced is variable, averaging from three to five years.

One of the greatest difficulties in the application of the method has been the inability to find any single or even multiple tests which will determine whether a favorable outcome is to be expected. The hypotensive effect of the administration of sodium amytal has been most extensively used to ascertain the drop in pressure to be anticipated as the result of operation. Some believe that when an adequate fall in pressure does not occur, the likelihood of success is poor, but that on the other hand, an adequate fall is no guarantee of success.

The precise mechanism of the action of these operations is not clear. It is probable that several factors play a part, among these being a reduction of venous return to the heart when the patient stands erect as a result of denervation of extensive vascular areas. Besides this the denervation of the large splanchnic area prevents the normal vasoconstriction from occurring when the patient moves from a horizontal to an erect posture.

5. *Kidney Extracts.*

Extracts of kidneys have been prepared which lower blood pressure and cause improvement in the clinical picture of patients, but the mechanism by which these extracts act is entirely unknown. The term "non-specific" has been employed to describe these actions. This may be true in the superficial sense of this word, i.e., the lowering of pressure is due to an unknown mechanism set into action by a heterogeneous group of substances. Among these is fever, but many patients have fever without reduction in arterial pressure, and a few vice versa. The important point to recognize is that if any form of therapy will lower blood pressure and benefit the patient, it does not make a great deal of difference what the mechanism is.

No altogether suitable extract has been prepared to date. There is some evidence which suggests but does not prove some degree of specificity. Kidney extracts will reverse the intra-renal hemodynamic effects usual in many cases of hypertension to a more normal one. Further, cardiac output will be elevated in hypertensives when the mean pressure falls. Work along this line is still in its embryonic stage.

6. *Excessively Low Sodium Diets.*

The use of low sodium diets has recently been revised but now the restriction is even more severe, often not more than 200 mg. of sodium allowed in one day's diet. This level is extremely difficult to attain in most patients and is altogether impractical for some. At least 25% of patients show a significant fall in arterial pressure and some feel better. Administration of salt in these cases is associated with a rise in blood pressure. It appears that there is some association between the change in salt content of the diet and the height of the arterial pressure in these particular patients. Rarely circulatory collapse occurs due to severe salt deprivation; hence the treatment has potential dangers. These can be exaggerated because most patients who are not in a hospital under rigorous supervision do not keep their salt intake below 0.5 gms. At best, it seems that relatively few patients are benefited by drastic salt restriction, but for these it may well be worth the effort.

The use of amberlite resins has been suggested as a short-cut to a salt poor diet. Oral administration of certain types

of these exchange resins should theoretically remove enough sodium from the intestinal juices to achieve the desired reduction in sodium balance. It is much too early to recommend their general use. It is possible that some resins may do serious damage by absorption of other electrolytes than sodium from the gastrointestinal tract.

7. *Rice Diet.*

There are few suggestions for the treatment of hypertension that have stirred so much controversy as the rice diet. At present it is not possible on the basis of published evidence to arrive at any considered opinion of its value.

The rice diet and the sodium depletion diet are alike in that each yields about 2000 calories of fuel value and contains less than 0.5 gms. of sodium. They differ in their protein content which in Kempner's regime is less than 20 gms., and in Kempner's assumption that other foods contain unidentified toxic substances not present in rice which embarrass the kidneys. In 1944 Kempner first reported on the use of the rice diet. It contains 2000 calories, not more than 5 gms. fat, 20 gms. protein, 200 mg. chloride, and 150 mg. sodium. From 250 to 350 gms. of rice (dried weight) is taken daily. All fruits are allowed except nuts, dates, avocados, dry or canned fruits or fruit derivatives to which substances other than white sugar have been added. White sugar and dextrose are allowed ad libitum; on the average a patient takes about 100 gms. daily but if necessary as much as 500 gms. may be used. Tomato and vegetable juices are not allowed. Usually no water is given and the fluid intake is limited to 700-1000 cc. of fruit juices per day. Supplementary vitamins are added — vitamin A, 5000 units; D, 1000 units; thiamin chloride, 5 mg.; riboflavin, 5 mg.; niacinamide, 25 mg.; calcium pantothenate, 2 mg. Some form of iron is desirable. Rest in bed is not desirable.

It is my view that the rice diet deserves much more careful study before its wide popularization by some of the leading clinics in the country. Our studies strongly suggest that the rice diet is essentially a low sodium diet. When blood pressure falls during its use, the addition of salt again raises the pressure.

It must be emphasized that this procedure is still in the investigational stage. The effects of the weight loss due to the diet has not yet been adequately evaluated. European experience during the war would suggest that these play a much more important part in determining the decrease in arterial pressure than deprivation of animal protein and provision of protein of vegetable origin.

8. *Rutin.*

The clinical usefulness of rutin seems to lie in its similarity to vitamin P or hesperidin. It is believed by some to be useful in "increased capillary fragility" in hypertension, in retinal hemorrhage, apoplexy, pulmonary hemorrhage and drug reactions. The effects of rutin cannot be adequately studied because of the wide variability of the results of the various tests of capillary fragility. Careful studies show that rutin has no significant effect on the hypertensive process. Next, rutin was used in the hope that cerebral hemorrhage might be avoided on the theory that hemorrhage is due to capillary bleeding but there is no cogent evidence in support of this theory. Clearly, the widespread sale of rutin by drug houses on the basis of published evidence was most unwise. Unless better evidence is forthcoming, rutin has no place in the management of hypertension.

9. *Bacterial Pyrogens in the Treatment of Malignant Hypertension.*

Daily administration of concentrated bacterial pyrogens, over periods of weeks or months often causes remarkable clearing of the pathological changes in the eyegrounds of malignant hypertensives. Arterial pressure is reduced and papilledema and retinal exudates disappear with this treatment. Improvement is also noticed in the electrocardiogram and the heart size diminished. Except for persistent elevation of arterial pressure, remissions last for an average of two years. The greatest drawback to this treatment is that tolerance to the pyrogen usually appears in 5 to 19 weeks after which arterial pressure usually rises to control levels but without re-

(*Continued on page* 24)

THE STRUCTURE OF THE LIVER OF CYCLOSTOMATA *

HERBERT BENGELSDORF, B.A. and HANS ELIAS, Ph.D.*****

Findings in human anatomy are of immediate interest because of their applicability to clinical medicine. Yet, we are not only interested in the dry description of our own species, the temporary end product of evolution and embryology. From a scientific standpoint, the question "From where does this structure derive?" is of great importance. This is not only an academic question but knowledge of comparative anatomy frequently is necessary to interpret anomalies and pathological phenomena.

Recent observations have revealed basic facts concerning the structure of the human liver. It is for the reasons mentioned above that a comprehensive study of the evolution of a human liver has been undertaken in the Anatomy Department of this school.

Introduction

The vertebrate liver has been described as a tubular gland. In mammals the tubules were said to be narrowed to cords, two cells thick (Figure 1). Two years ago (Elias, 1948, 1949 a, b) this concept was shown to be untenable and it was demonstrated that the mammalian liver consisted of a system of anastamosing plates, one cell thick, which surround lacunae in which the sinusoids are suspended (Fig. 2).

This finding raised the question of the evolutionary origin of these mammalian liver plates (laminae hepatis). In order to find the structural patterns which preceded the laminar one, the investigation was begun on the most primitive of the vertebrates, the cyclostomes.

The Cyclostomata are divided into two orders: 1. *Myxinidae* (hagfishes) can be recognized as the most primitive cyclostomes since they carry the pronephros into adulthood. 2. *Petromyzonidae* (lampreys) are more advanced than the Myxinoids, their adult kidney being the mesonephros. Ammocoetes was the name given by older zoologists to the larvae of the lampreys at a time when their larval nature was not recognized. The Ammocoetes are even simpler in structure than the adult hagfishes. Some modern zoologists believe that the first vertebrate was very similar to Ammocoetes.

A survey of the literature reveals that the livers of all vertebrates, including those of cyclostomes, have been described as tubular glands. Braus (1896) calls the myxinoid liver a tubular gland, the tubules of which end blindly and do not unite into nets. Holm (1897) supports this view and adds that the liver of Myxine "approximates greatly in its structure that of the submaxillary gland of mammals." Brachet (1897) in describing the liver of Ammocoetes, the larval form of the Petromyzonidae, says it is a "true liver similar to that of the higher vertebrates, that it is made up of ramifying secretory tubules."

Observations

I. *Myxinidae*

If the Myxine liver actually conformed to Braus' verbal description, we would expect to find in histological sections, many cross sections of tubules as well as some oblique and perhaps a few longitudinal sections of tubules. Indeed, if one examines an actual section of the liver of Myxine glutinosa, no cross sections of tubules are to be found (Fig. 4). Instead, one finds a pattern remarkably similar to that of the mammalian liver. In order to determine whether, in the 12 micron section shown in Figure 4, a large number of tubules have been cut longitudinally, or if this organ has a laminar structure, it is necessary to examine a thicker section. By focusing up and down through such a section it is now possible to make a drawing (Fig. 5) which demonstrates the continuity of the parenchyma and the manner in which the hepatic walls surround the sinusoids.

A wax reconstruction (Figs. 6 and 7) again demonstrates three-dimensionally the existence of hepatic walls and the absence of tubules. Figure 6 shows the top

---

* Presented at the 63rd meeting of the American Association of Anatomists in New Orleans, April 7, 1950.

** Department of Anatomy, The Chicago Medical School.

*** Assistant Professor of Microscopic Anatomy, The Chicago Medical School.

surface of the reconstruction where the sections of the walls can be seen as they are cut transversely and tangentially. Figure 7 portrays an interior view of the model after it has been broken apart, showing the continuity of the walls.

The hepatic walls of Myxine glutinosa are two cells thick while the mammalian plates are only one cell thick. The basic structural pattern, however, is the same.

II. *Petromyzonidae*

The same methods were applied to the Ammocoetes. Since these forms are considered to be even closer than Myxine to the primitive vertebrate ancestral stock, it was thought that they might shed some light on the evolutionary origin of the laminar liver. In considering these animals, however, it must be remembered that they are the larval form of the Petromyzonidae which have been described by Shore and Jones (1889) as having an atypical, ductless liver, in the adult stage.

Ammocoetes from two sources were studied. The first collection, kindly donated by Mr. Loren P. Woods of the Chicago Natural History Museum, included two genera, Ichthyomyzon and Petromyzon, species unidentified. These specimens are the ones referred to in the following discussion. A second group, for which we are grateful to Dr. Richard Weissenberg of the Women's Medical College of Pennsylvania, consisted of five specimens of Petromyzon marinus from the Salmon River near Pulaski, New York.

As in Myxine, sections of livers of young Ichthyomyzon, 4 to 6 centimeters in length, show no evidence of the existence of tubules, i.e., no cross sections of tubules can be found. The long, connected rows of hepatic cells indicate a laminar structure (Fig. 8).

However, in sections of livers of Ichthyomyzon measuring from 15 to 17 centimeters in length, as many cross sections of tubules are found as one would expect to see in a tubular gland (Fig. 9). A wax reconstruction confirms this interpretation. Figure 10 shows the top surface of the model with the cross sections of tubules visible. The group of tubules in the lower part of the picture is not attached to the adjacent network, and if this group is removed, the interior of the model (Fig. 11) shows the ramifying tubules.

Intermediate stages possess a transitional liver containing both plates and tubules (Figs. 12, 13, 14). The laminar area is sharply delimited from the area which contains tubules in this Ammocoetes of the genus Petromyzon, species unidentified.

The five Petromyzon marinus Ammocoetes, varying in length from 5.5 to 11 centimeters, also demonstrate a transition from laminae to tubules. The change, however, is a more gradual one. The walls throughout the entire liver break down individually into tubules (Fig. 15), and there is no sharp line of demarcation between the two patterns at any stage of development. Actually both patterns are present in each of the five Ammocoetes in this series, but the relative number of tubules increases while there is a decrease in the relative number of laminae corresponding approximately to the increasing length of the specimens.

Bearing in mind the status of the adult organ, it is apparent that the tubular liver of the older Ammocoetes is, itself, a transitional form in the metamorphosis of this organ from its laminar structure into that of an atypical ductless gland.

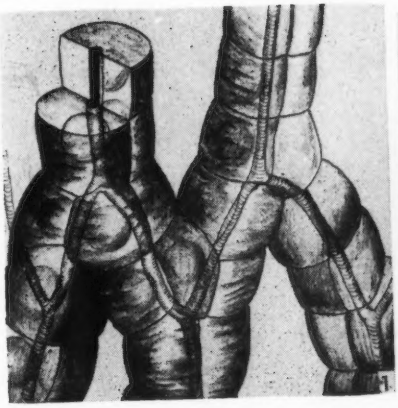
Conclusions

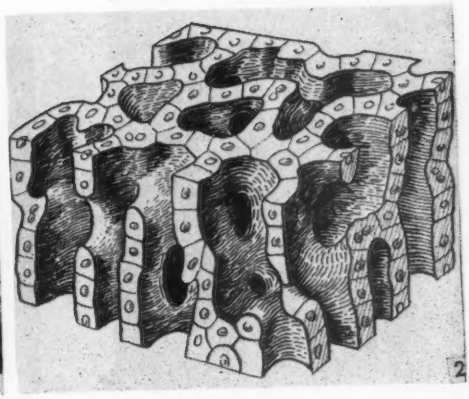
The search for the evolutionary origin of the laminar hepatic architecture must now turn to the prevertebral forms since it has been shown that this structural form of the liver already exists in the most primitive of the vertebrates, the cyclostomes.

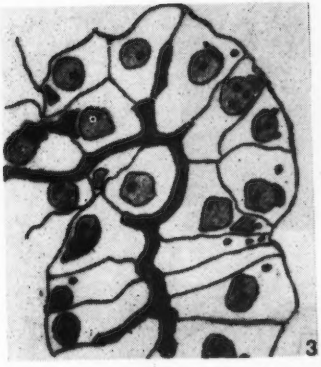
Summary

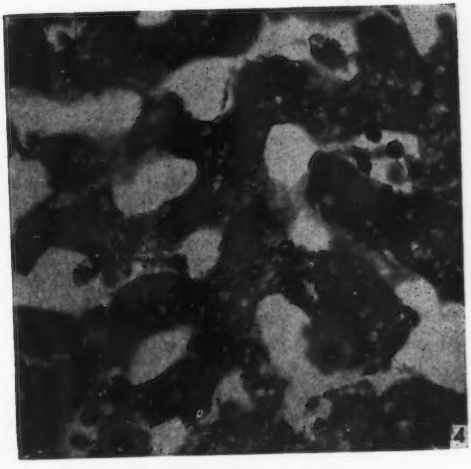
The liver of the Myxinidae resembles in its structure that of the mammals. It consists of walls separating sinusoidal lacunae. These walls are two cells thick, differing from the one cell thick mammalian plates.

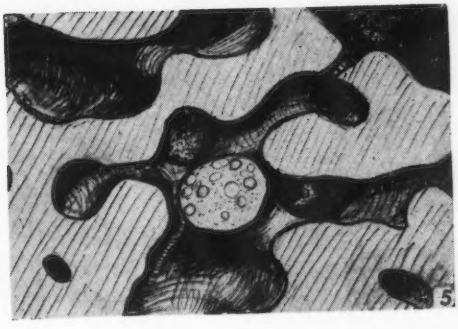
The liver of the Petromyzonidae has, in early Ammocoetes larvae, a laminar construction similar to that of the Myxinidae. It passes through a tubular, transitional phase while undergoing its metamorphosis into the ductless gland of the adult Petromyzonidae.

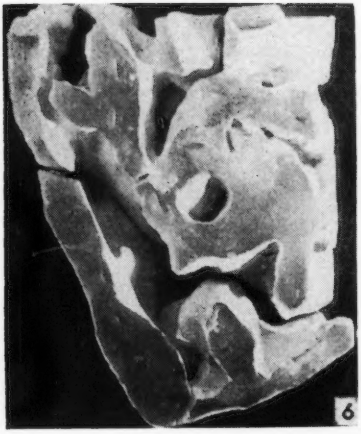


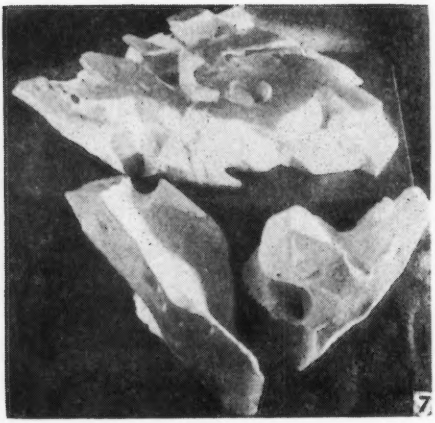


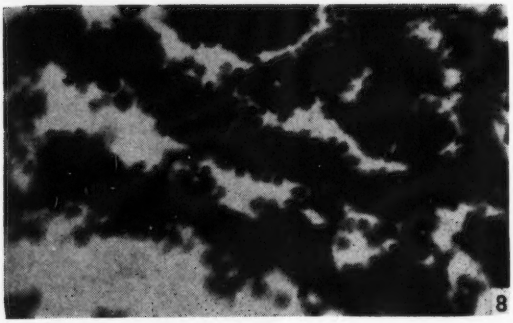


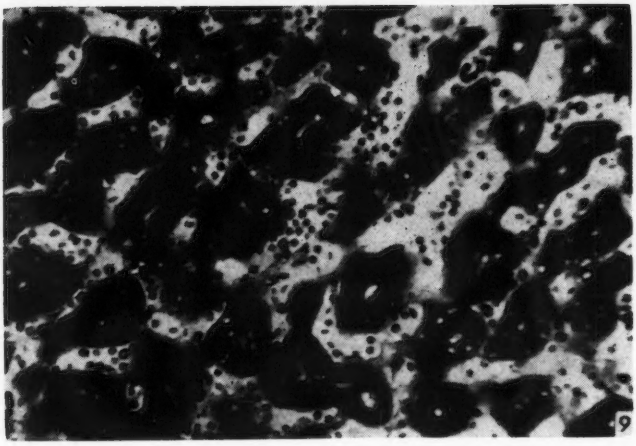


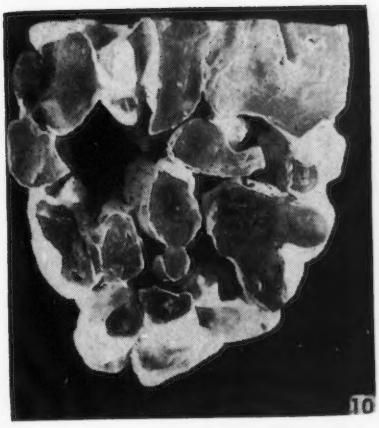



6


7

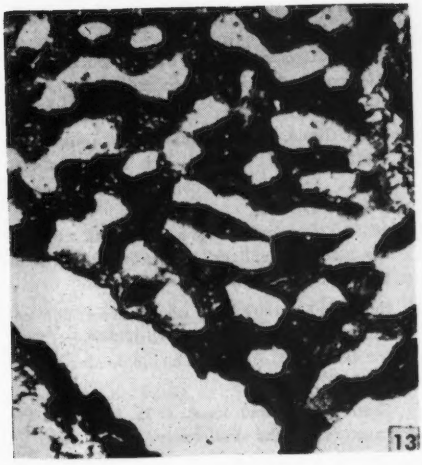

8


9

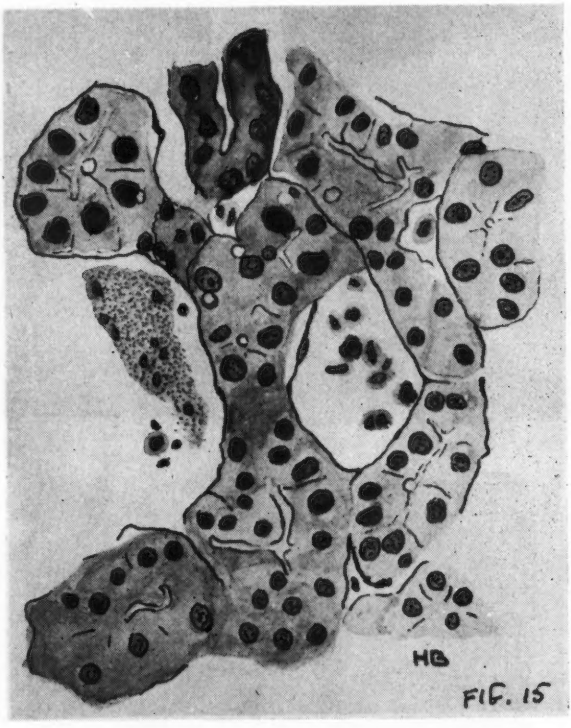

10


11


12


13


14



EXPLANATION OF FIGURES

1. Stereogram of liver cords. After Elias 1949a.
2. Stereogram of anastamosing hepatic plates. after Elias 1948.
3. Drawing by Braus of liver of Myxine glutinosa.
4. Liver of Myxine glutinosa X 400.
5. Thick section of liver of Myxine glutinosa.
6. Wax reconstruction of liver of Myxine glutinosa.
7. Interior of figure 6.
8. Liver of 5 centimeter Ammocoetes.
9. Liver of 16 centimeter Ammocoetes.
10. Wax reconstruction of liver of 16 centimeter Ammocoetes.
11. Interior of figure 10.
12. Transitional stage in metamorphosis of Ammocoetes liver.
13. Detail of laminar area in figure 12.
14. Detail of tubular area in figure 12.
15. Liver of 10.7 centimeter Petromyzon marinus showing transformation of laminae into smaller pieces of tissue resembling tubules.

REFERENCES

1. Brachet, A. 1897 Development du foie et pancreas de l'Ammocoetes. Anat. Anz., *13:* 621-636.
2. Braus, Hermann. 1896 Untersuchungen uber die vergleichende Histologie der Leber der Wirbeltiere.
3. Elias, Hans. 1948 Beobachtungen uber den Bau der leber. Anat. Nachr. *1:* 8-20.
   1949a. The liver cord concept after 100 years. Science 470-472.
   1949b. A re-examination of the structure of the mammalian liver. I. Parenchymal architecture. Am. J. Anat. *84:* 311-334.
4. Holm, J. F. 1897 Uber den feineren Bau der Leber bei den niederen Wirbe!tieren. Zool. Jahrb., Abt. f. Anat. & Ontogenie der Thiere. *10:* 277-286.
5. Shore, T. W., and Jones, J. L. 1889. On the structure of the vertebrate liver. Jour. of Physiol. 10: 408-428.

THE MEDICOLEGAL ASPECTS OF BLOOD TRANSFUSION*

DR. LEONE LATTES, M.D.**

The question of the physician's professional responsibility has always been relative. Judicial authorities have consistently recognized that malpracitce does not involve small faults, or "aquiliae," but only serious, inexcusable errors. Otherwise, the orderly exercise of the medical profession would become impossible as doctors would be continuously exposed to claims from dissatisfied patients.

Malpractice is a crime recognized by penal law just as is homicide or injury by civil fault. The negligent doctor, who disregards the elementary precautions required by law and common sense, fails in his civil responsibility. To establish the existence of a civil misdemeanor, it is necessary to prove incompetence and lack of diligence, below the norm of reasonable ability or common sense. A decision based upon the skill and competence of exceptionally expert doctors would be unfair. The evaluation of medical responsibility must be based upon experience of what constitutes normal and reasonable action under any given circumstances and is, therefore, within the range of admissible error. Where new technics are involved, this boundary line has not been well established and the physician must be given greater freedom of judgment, for there are no precedents upon which he can base a decision. Opinions concerning medical responsibility change rapidly as technics improve, so that an act which at one time might be considered unavoidable might, at another time, constitute malpractice. Conditions and environment also influence judgment of the physician's responsibility. It is not possible to compare, for example, the facilities available to the city doctor, with those available to the rural doctor.

For many years the basic concepts of medical responsibility, with regard to blood transfusion, remained in the preliminary stage. This was because blood transfusion was a relatively new procedure, and standardized rules were a mere speculation.

It is clear that when an official rule exists, its transgression constitutes malpractice, unless the offender can demonstrate that the particular circumstances were beyond his control.

The first problem is whether the specific transfusion was indicated. From the medicolegal point of view, this problem poses two clinical questions:

(1) Was there absolute indication for the transfusion?

(2) Was there any absolute contra-indication?

Since the judge is not competent to evaluate therapeutic procedures, it is clear that the doctor's decision for a transfusion could never be questioned in court if the matter were one of relative indication or contraindication, because precedents could easily be found in the literature showing that, in similar cases, transfusion was harmless. Furthermore, in many conditions, such as heart and renal disease, the risk lies not in the transfusion itself, but in the way in which the transfusion is made. This means that some of the so-called "absolute" contraindications are actually relative ones. However, it can be charged that the doctor's action was careless and imprudent; that the transfusion was given lightly and empirically without careful and accurate examination of the patient and without having carefully weighed the risk involved.

At this point the problem arises of determining where the responsibility lies—with the physician who prescribed the transfusion or with the physician who merely carried out his orders. Sudden death, occurring after a transfusion which had been properly prescribed and given, must be due to predisposed conditions in the patient. The morbid conditions are part of a pathological complex of the patient and must be ascertained by the attending physician. On the other hand, harmful consequences of transfusion

*Lecture delivered at The Chicago Medical School.

** Professor of Forensic Medicine, University of Pavia, Italy.

could be due not to a disease proper but to unknown predispositions or idiosyncrasies which do not appear during ordinary examination. These latent predispositions could, in certain cases, clear a careful and scrupulous physician of all responsibility. In any case, the man who administers the transfusion cannot be held responsible where he is called in as a technician with very limited freedom of action, for in such a condition the transfuser is only the executor of orders received from a colleague. The attending physician is responsible for his own staff, who execute his orders not only when their work is correct, but also when it is erroneous or incongruous.

I should like to examine now the opposite side of the question; namely, the responsibility for not performing a transfusion which was clearly indicated. This would be a case of negligence by omission.

However long the list of indications for transfusion, however outstanding its successes, I believe that, with one exception, there are no absolute indications for it, and therefore, there can hardly be guilt by omission. In my opinion, only one pathological situation constitutes absolute indication for a transfusion, and its omission can be guilt. This is acute hemorrhage. This problem came to my attention twice. The first time was many years ago and the case is most typical. A hunter was wounded in the arm by a gunshot which pierced the humeral artery. A guide applied a string to the arm immediately, and the wounded man was brought to the hospital. The tourniquet had been badly applied and allowed the blood to leak. When the wounded man arrived at the hospital, he was profoundly anemic and had a very weak pulse. The artery was ligated and the patient given hypodermoclysis. Nothing else was deemed necessary, and the patient died during the night of acute anemia. The family complained about the doctor's behavior but did not make a legal claim. That was twenty-five years ago, when blood transfusion was not yet widespread and there was no organization for it. For this reason, the carelessness of the doctor would, in part, be excused. Today, a similar case would be considered inexcusable. It must be well understood that the omission in itself cannot be considered by the courts, but only in relation to the circumstances of time and place and available means.

The second medicolegal case of omission developed into a full-fledged judicial case. A little girl, four years old, was operated upon by a pediatrician for adenoids. After the operation, the child continued to bleed despite all attempts at hemostasis. After many hours the pediatrician consulted a throat specialist, who found the persisting hemorrhage due to incomplete operation. He completed the operation, stopped the bleeding, and advised hospitalization for the child. During the night, the little girl died even though a hypodermoclysis was performed. The principal charge, when the case was brought to court, was omission of transfusion. Experts had found that the intestine, not the stomach, was filled with blood and they concluded that death was due to nasopharyngeal hemorrhage and that a transfusion certainly would have saved the patient. I had to express an official opinion of this case. I pointed out that death was not due to the actual amount of blood lost, but to secondary hemorrhagic shock, and that this shock appeared later and could not have been noticed by the physician during the period of observation. When the doctors left the hospital for the night, the little girl was in satisfactory condition, and there were no specific indications. Therefore, while a transfusion might have been "useful," it was not indispensable. I must point out that this case also happened several years ago when routine transfusions were not given. In the latter case, a question was raised whether the responsibility belonged to the pediatrician or to the specialist who, in completing the operation, had really stopped the hemorrhage (as shown by the fact that there was no blood in the stomach). The prosecutor asked for conviction of the pediatrician, but the court acquitted both doctors and stated that it found no professional negligence. This judgment did not modify my opinion that the responsibility devolved upon the doctor in

charge, rather than upon the technician. In this case we must emphasize the always very important fact that, when an accusation of omission is made, the patient's condition must not be judged from the late period or from the post-mortem examination, but must be considered as it appeared at the moment when the therapeutic decision was made.

A second point concerns the choice of the blood to be transfused. It is now generally known that dangerous and harmful donors do exist. The harmful donors can be divided into two groups: (1) incompatible blood types and (2) infectious or intoxicating, although not serologically incompatible. Incompatibility derives from serological heterogeneity and is expressed by the well-known rule of Ottenberg: *The receiver must not contain antibodies which react with antigens of the donor.* Here, one must distinguish between preformed antibodies of the ABO system and those due to previous iso-immunization by pregnancies or transfusions. From the point of view of legal responsibility, the danger of immunity due to antigens of the subgroups A_1, A_2, and MN is insignificant. On the other hand, recently acquired knowledge of the Rh system creates new and serious problems of medical responsibility. It compels the doctor to study carefully the transfusion history of any candidate for a transfusion, because former transfusion can leave immunizing traces. Furthermore, it is necessary for women to have a careful obstetrical history, taken to discover possible miscarriage, premature births, jaundice or hemolytic illness of the new born, which might be clues to the presence of iso-immunization. Whereas, in a male, the first transfusion is never dangerous, because of Rh substances, it may be dangerous in a pregnant woman. Therefore, in the case of repeated transfusion of pregnant women, or in the newborn, one cannot limit the investigation to the ABO system. It is indispensable to check the Rh compatibility also, within limits dictated by the urgency of the circumstances and by laboratory facilities. In many cases, it is imperative to seek negative Rh donors disregarding the possibilities of Hr immunization. Today, it is not permissible, and would be legally punishable, to perform an incompatible transfusion, even in an emergency, without serum examinations.

It has happened and continues to happen that, despite all tests, incompatible transfusions are given, either because the test result was wrong, or because one group was confused with another. The latter case is simpler, judicially speaking, and it is usually not difficult to find the responsible person. Often the confusion is due to the double nomenclature of the groups which should be abolished in favor of universal adoption of the international ABO system. It is obvious that confusion between groups I and IV, of Jansky and Moss, can be disastrous. There is the case of a practitioner who asked for a donor from Group I, being convinced that it corresponded to the group A, because that was the first letter of the alphabet. Only by a fortunate chance was the error discovered before transfusion. Furthermore, there always exists the possibility of clerical error in recording the blood group of the patient. In this case, the responsibility is clear.

The case of a real mistake in the determination of the blood group, or type, is different and, to judge whether or not the mistake is excusable, one must analyze the causes. These can be of three types: (1) defects in the quality of the diagnostic sera, (2) errors in performing the reactions, (3) intrinsic serum peculiarities of the examined blood. Regarding the first condition, it is easy to say that specific sera must meet high qualifications, but in a hospital or in private practice it is not so easy to check whether or not these qualifications are met. I recall a case in which I was asked to give medicolegal advice. It was a case where incompatible blood AB was given to a patient of Type A. This was because the test serum, anti-B, had practically lost its activity, causing the AB blood to be diagnosed as A. The perfectly reliable institute, that had provided the serum, withdrew the lot as unusable, even though the lot had not reached its expiration date. The transfuser could not be responsible for a mistake of grouping, since he had used a well-known product,

within its date of expiration, and according to enclosed instructions. Under these conditions, the mistake was inevitable. On the other hand, the institute stated that control samples of the batch were still active and that the loss of activity in the other units was due to unknown reasons, probably the manner in which the serum had been stored by the druggist. In this case, the responsibility of the manufacturer was challenged for having marked on the boxes a date of expiration about which little is known, thus giving the doctor a false feeling of safety. The case was dropped, but the manufacturer stopped printing expiration dates on its diagnostic sera, leaving to the user the resonsibility of making the necessary controls.

A question can now be asked! What is the minimum necessary caution and diligence in the use of test sera which will relieve the physician of responsibility for errors? It is necessary to start with the assumption that the doctor who performs the preliminary examinations must be convinced that he is using efficient diagnostic sera. Consequently, he can only be blamed for errors of technic. An isolated general practitioner cannot be required to control the activity of the sera, as this would limit excessively the possibility of transfusions. In large institutions and hospitals where transfusions are made frequently, the omission of such controls would, instead, be considered carelessness.

The controls are limited, as a rule, to testing the agglutination of the red cells of the donor and the recipient, or of the donor only, when a universal donor is used. If both tests with Anti-A and Anti-B sera are negative, the average physician can state that he is dealing with a universal donor. If the sera are very active, can a mistake in grouping be excused? A gross mistake, such as the exchange of an A with a B, or with an O, cannot be excused, as it can only happen due to negligence or lack of skill. We can excuse a mistake due to condition of the blood not easily detectable such as hypoplasia of some agglutinogens. This is found in bloods A_2 and, especially, in A_2B, which can easily be confused with B. Sometimes this differentiation requires exact and careful testing by an expert serologist and cannot be expected of the general practitioner, nor even of one with great transfusion experience.

More delicate still is the problem of Rh. The doctor cannot possibly be expected to check all the types of the Rh system, and probably not even to perform the delicate tests for a possible immunization. Anti-Rh standard serum is now readily available and is comparatively easy to use, so that failure to identify Rh negative donors (standard) could, in effect, be considered inexcusable when their use is an absolute necessity. The conditions in which the ordinary doctor finds himself is different from that of those who are required by law to use special diligence: that is, the big hospital, and the organizations of donors or the blood banks. These must keep books, where donors of the various groups and types are permanently registered. These organizations can rightly be expected to avoid all mistakes by availing themselves of independent examinations with different diagnostic sera or double checking of the agglutinogens and the agglutinating power of the sera. The blood 0 (universal donor) cannot only be identified by negative tests but also by the positive demonstration that its serum contains the two antibodies Anti-A and Anti-B. This test must be quantitative and is indispensable in order to eliminate the so-called dangerous universal donor: that is, the donors too rich in antibodies. It would be reproachable negligence on the part of the organization to omit the titration in the case of habitual donors. In any case, it is clear that any irregularity in the results of the various tests must automatically lead to the elimination of the donor, especially when it is impossible to study his individual characteristics in detail.

Before accepting a donor, one must bear in mind not only the blood compatibility but also the possible existence of contagious disease. Special attention must be given to syphilis, tuberculosis and malaria which must be ruled out by means of clinical examination and routine serological reactions. The complete

omission of this check, when the condition for its execution are available, is to be considered as guilty carelessness. Nevertheless, in case of emergency, the matter of infection becomes secondary. It is evident that if there is no time for tests other than that of blood compatibility, the doctor will not be responsible even if contagion occurs. To avoid the worst of the two evils, death, one must take the minor risk of a syphilitic or malarial infection which will be taken care of later. This is an evident case of necessity as juridically defined. In another category are the allergic manifestations, which generally cannot be foreseen. Among these accidents of anaphylactic type are the very rare cases of pulmonary edema following transfusion. As no precaution can be taken with certainty to prevent it, this complication must be considered as beyond control.

Technical mistakes can be made in the performance of transfusions. Generally, a transfusion is not a difficult intervention. On the contrary, it is rapidly becoming so simple as to make it accessible to an ever larger number of practitioners. However, to perform it correctly, one must acquire a minimum scientific and technical skill. Anyone who sets about making a transfusion without this minimum of theoretical knowledge and without being familiar with the technics involved, can be charged with neglect or recklessness in case of complications. There are difficulties of technical nature, such as the one connected with any intravenous injection. These involve a risk for the donor as well as the recipient. Generally, and excepting unavoidable accidents, an incorrect intravenous injection is a sign of lack of skill. Of course, there are cases in which excessive fat, abnormally small veins, and other local abnormalities make the transfusion difficult. In these cases, the cautious operator must decide whether an incision of the skin is indicated. This, of course, entails precautions inherent to surgical procedures.

In the performance of the transfusion, the introduction of air into a vein, and, still worse, a gas embolism, must not happen. The same can be said for a blood-clot. Should they happen, the physician cannot escape the charge of lack of skill. When stabilized blood is used, one is faced with the problem of how long blood can be preserved outside the body. No absolute rule can be given here. Obviously, it would be dangerous to transfuse stored blood which has been collected with excessive agitation and foaming, or has been stored in improperly closed containers or at high temperatures and might be contaminated, hemolyzed, or altered in its morphological elements. It is certainly a serious omission not to ascertain the state of preservation of the blood by proper means.

Two points must be made regarding the transfusion itself. The first one concerns the so-called preliminary biological test, or Oelecker's test, consisting of a preliminary transfusion of 20 cc. to 30 cc. of blood. This procedure, once considered advisable, has become now an absolute necessity for scientific and clinical reasons. As said above, the serological tests prescribed for the choice of the donor do not reveal every possible individual incompatibility, especially in cases of repeated transfusion. The only efficacious precaution to avoid complication is the clinical one represented by the preliminary biological test. Its omission must be considered contrary to elementary technical rules.

The second point refers to the rate of transfusion. It is of little importance in small transfusions of 100 cc. to 200 cc., but it must be taken into serious consideration in case of large transfusions of a pint or more. In this case, excessive speed can cause a sudden overloading of the recipient and results in cardiac failure.

The tests for indications and contraindications, the choice of the blood donor and the performance of the transfusion, are the foundations on which responsibility is based. Furthermore, in the case of a trial, ordinary medicolegal arguments come into the picture. Careless or imprudent behavior is not sufficient to create penal and civil responsibility unless it is proved that this carelessness is the cause of the damage, and the pathogenic connection between the damage

and the mistake which was made. It would be a great medico-legal and juridical error to assume transfusional guilt only because the damage followed the transfusion. The existence and the extent of mistakes on the part of the physician or the serologist must first be demonstrated, as serious manifestations can follow even a transfusion correctly prescribed and performed.

I will only mention, at this point, the difference which is always discussed in legal medicine between coincidence, occasion, concomitant cause, and exclusive cause. These concepts are not always clearcut and a careful analysis must be made. If an emotional person dies suddenly at the moment when the needle is introduced into the vein or at the sight of his blood, nobody can say that the death was caused by the transfusion, but only on its occasion.

Even if, theoretically, the occasion belongs to the constellation of the causes from the medicolegal and judicial point of view, it is clear that it does not possess a positive pathogenic conection; so much so that the unfortunate result must be considered as an unavoidable accident, substantially determined by personal conditions, not identifiable beforehand. In cases of death, one must establish the following points:

1. If any incident happened which was intrinsically adequate to determine death.
2. If death was associated with the characteristic symptomatology of transfusional death.
3. If pathological conditions existed which could be considered concomitant causes or only causes of death, and if these could have been revealed by preventive clinical tests.

Only with a knowledge of all these factors can the expert solve the problem of whether the transfusion contributed to the death or was only the simple imponderable occasion.

At any rate, in the majority of cases, transfusional responsibilities are beyond the field of the contract, or "culpa aquilia," and the burden of proof belongs to the damaged party. It would be hardly possible to convince the court that the damage arose from the violation of a tacit contract. This is an advantage for the doctor, since, outside the contract, the fault is not legally presumed and transfusional responsibility can be affirmed or proved only in cases of gross professional inadequacy.

In this manner, the worthy work of the physician will not be paralyzed by the fear of being sued for accidents which were due to the nature of the patient, or his illness, or to more or less known idiosyncrasies, and were at any rate, beyond control. The physician will be free to carry on in his necessary and humanitarian activities without undue preoccupation.

BIBLIOGRAPHY

Galassi, N.—First International Congress on Blood Transfusion, Rome 1935.

Lattes, L.—Second International Congress on Blood Transfusion, Paris 1937.

Fomertano, V.—Ibid.

Cattabeni, M.—National Congress on Blood Transfusion, Milano 1947.

Lattes, L.—Dia Medico, Buenos Aires 1940.

Carnelutti, F.—Arch. Antrop. Crim. e Med. Leg. 1938. Italian Ministry of Inter.—Decree, June 3, 1935. German Ministry of Justice and Interior—Decree, May 26, 1937. Regulations Governing Blood Donors and Blood Banks in New York, Sanitary Code, Section 108, Nov. 21, 1930 and March 14, 1939

British Medical Research Council—War Memorandum on Determination of Blood Groups, N. 91943/44.

Reglamento de la Ciudad de Buenos Aires sobre Transfusion Sanguinea Plasmoterapia, N. 13733/45.

VAGARIES OF AUTONOMIC PHARMACOLOGY

JAY A. SMITH, Ph.D.*

The wealth of new synthetic drugs has led to further exploration into the pharmcology of the autonomic nervous system. As such exploration continues, it is only natural that much is contributed toward understanding the method of action of this system, and also as a direct result, many inexplicable details are discovered. As research continues, the unexplained points are gradually explained, but more inexplicable details continue to be found. Thus, although a great deal is known about the pharmacology of the autonomic system, many vagaries exist at the present time.

The classical concept of the pharmacology is illustrated in Fig. 1. The peripheral nervous system, as a whole, is divisible into two general parts, the somatic system, and the autonomic system.

The somatic nervous system may be regarded as a series of nerves, synapsing at strategic points with other nerves, and communicating with the muscle at the neuromuscular junction. One theory that holds the attention of many at this time is that acetylcholine is involved in the production of the nerve impulse along the nerve fiber[1] and at the neuromuscular junction; indeed, "all facts support the assumption of the generality of the role of acetylcholine in all nerve tissue."[2]

The autonomic nervous system is divisible, largely by anatomic means, into the sympathetic system and the parasympathetic system. Both systems may be regarded as consisting of preganglionic fibers, ganglia, post-ganglionic fibers, post-ganglionic endings, and effector materials within the effector cells.

The pre- and post-ganglionic fibers themselves undoubtedly utilize acetylcholine in the process of transmission. Blocking these fibers directly is difficult, possibly because of a chemical barrier,[2] but it may be accomplished by an anaesthetic such as procaine applied locally.

The sympathetic ganglia are located in the well-known chain at a distance from the organs and structures they supply. The parasympathetic ganglia, on the other hand, are located, for the most part, within the organ or structure they supply. Both utilize acetylcholine in transmission.[3] Nicotine, in small doses, stimulates the autonomic ganglia and neuromuscular junctions; hence the action of acetylcholine at these points is called the "nicotinic effect" of acetylcholine. Many substances block the autonomic ganglia, of which curare and tetraethylammonium salts are the best examples. Guyton and Reeder[4] show that about one and a half times as much curare is required to paralyze parasympathetic function, and five to ten times as much to paralyze sympathetic function as that required to paralyze skeletal muscle.

Post-ganglionic parasympathetic endings liberate acetylcholine and undoubtedly utilize acetylcholine in the process of transmission. Since muscarine stimulates these endings, the action of acetylcholine at these sites is said to be the "muscarinic effect" of acetylcholine. The classical blocking agent at these post-ganglionic parasympathetic endings is atropine.

The post-ganglionic endings of the sympathetic system may be divided into two classes: the "adrenergic" endings liberate sympathin and the "cholinergic" endings liberate acetylcholine. The cholinergic endings are blocked by atropine and stimulated by muscarine; therefore they display the muscarinic effect of acetylcholine.

The adrenergic endings may be divided further, depending on the effect they produce or the type of sympathin they liberate. One type of ending, such as that supplying arterioles, the capillary bed, and those muscles of the iris that produce dilation, responds with an excitation to sympathetic nerve stimulation; it supposedly liberates an "excitation" sympathin or "sympathin E." The other type of ending, such as that supplying the

* Assistant Professor in the Department of Physiology and Pharmacology, The Chicago Medical School.

gastro-intestinal tract and the bronchioles, responds with an inhibition to sympathetic nerve stimulation; it supposedly liberates an "inhibitory" sympathin or "sympathin I." The effects of sympathin E may be blocked by dibenamine and some of the ergot products, such as ergotamine, except for excitatory effects on the heart.[5]

The effects of the blocking agents is not to interfere with the liberation of the transmitter substance, be it acetylcholine, or sympathin, but rather to prevent the transmitter from exerting its effect. This is illustrated by curare; McIntyre[6] shows (page 105) that acetylcholine is liberated by curarized motor end plates. Dale *et al*[7] reviews the entire problem fully; Brown and Feldberg[8] show that acetylcholine is liberated from curarized ganglia. Acheson[9] points out that acetylcholine produces a depolarization at the motor end plate and that curare is capable of preventing this depolarization.

The above is a very brief discussion of the classical concept of autonomic function. As I mentioned in the introduction, a number of facts have been uncovered by diligent investigators which do not fit the neat scheme outline above. The remainder of this paper will deal with these autonomic vagaries, in the hope that the casual reader may realize that there are many points of disagreement, and have his attention directed to the fact that we are dealing with living biological material whose complexity still defies a complete understanding.

As a point of approach, consider the action of curare. According to the classical concept outlined above, curare blocks the nicotinic effects of acetylcholine, that is, it acts at the ganglia and at the neuromuscular junction. However, Luco and Altamirano[10] show that curare in large doses will block the effects of acetylcholine on the submaxillary gland, preventing saliva formation by post-ganglionic stimulation. Luco and Meza[11] show that an electrical stimulation of a post-ganglionic parasympathetic fiber can be blocked by curare, and they[12] contend that curare may inhibit all transmission of the cholinergic type. The conclusion should not be dismissed that curare may, in proper dosage, act to block the muscarinic effects of acetylcholine.

The curariform drugs themselves show certain interesting facts that do not fit into the classical picture readily.

Thiamine, usually regarded as a beneficial vitamin, can be toxic if given intravenously in large quantities[13] because it is a curare-like drug[14,15] in toxic doses. This fact might be astonishing except that Craig[16] lists literally hundreds of substances that manifest curariform activity.

Curare seems to be a potent liberator of histamine. Alam *et al*[17] and Rocha e Silva and Schild[18] show that curare liberates histamine from histamine stores and that curare itself is not a histamine-like material. Grob and associates[19] present photographs showing the "histamine wheals" resulting from subcutaneous injection of curare; these wheals could be reduced or prevented by benadryl. Landmesser[20] recorded blood pressure and measured bronchial caliber, and found that several curare preparations caused hypotension and bronchoconstriction; antihistaminic substances could prevent the bronchoconstriction, but did not alter the hypotension. Foregger[21] reviews several fatalities from the use of curare even when artificial respiration was applied. There seems to be no doubt that liberation of histamine and the bronchospasm it may produce is a complication in the use of curare.

Since curare materials generally act as blocking agents, it might be expected that they act universally as blocking agents. This does not seem to be the case with the central nervous system. Smith and associates[22] describe an experiment during which the intrepid Dr. Smith received enough curare to produce complete paralysis of all skeletal muscles; after recovery he reported that there was no impairment of memory, intelligence, or the sensorium; vision was adequate if the eyes were opened and the object moved into his line of sight; hearing was excellent. They conclude that d-tubocurarine has no central stimulant, depressant or analgesic effect.

Berry and Forster[23] report that curare applied directly to the cortex of cats in-

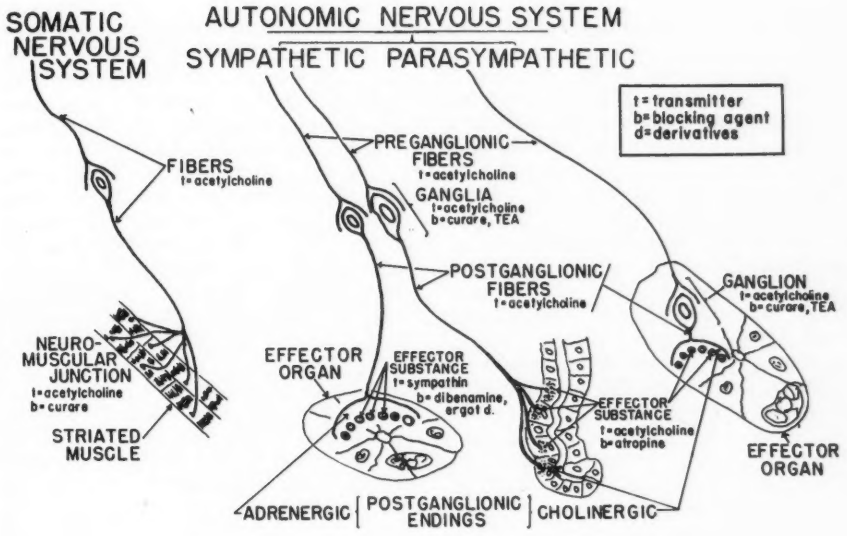


DIAGRAM OF AUTONOMIC PHARMACOLOGY

Jay A. Smith, Ph.D.

creases the activity of the electroencephalogram; Salama and Wright[24] show that d-tubocurarine applied to the surface of the brain excite respiratory, vasomotor and salivation centers; Minz and Veil[25] report that decerebrate rigidity is reduced by orthocurare. Feitelberg and Pick[26] report that in the frog, curare reduced brain waves, and McIntyre and associates[27] show that in dogs d-tubocurarine at first increases, then decreases electrical activity of the brain. McCawley[28] concludes that d-tubocurarine by rapid intravenous injection can produce central nervous system stimulation which may be, in turn, prevented by central nervous system depressants. Furthermore, he shows that with very large doses, curare causes an irreversible depression of the central nervous system, which may be temporarily reversed by metrazol.

Another ganglionic blocking agent already mentioned is tetraethylammonium or TEA, whose properties are discussed in detail by Moe and Freyburger.[29] Acheson and Moe[30] describe its blocking effects on autonomic ganglia. Luco and Marconi[31] show that TEA also will block post-ganglionic parasympathetic fibers to the pupil of the eye of cats. Thus TEA, in proper dosage, will block any cholinergic endings. Yet, it stimulates the neuromuscular junction, behaving like a veratrinic drug,[32] possibly by sensitizing the muscle cell to acetylcholine.[33]

Although TEA is considered to be a ganglionic blocking agent, certain cardiac sympathetic pathways are not blocked by it. Pardo, Rennick and Moe[34] isolated and stimulated pre-ganglionic sympathetic fibers and found that TEA blocks stimulations to the sinus node, but does not block those to the auriculoventricular node; this suggests that impulses to the A-V node traverse pathways which reach the heart without synaptic interruption.

The pharmacology of cholinergic endings includes a number of irregularities

or vagaries. Stimulation of the vagus classically slows the heart and produces a fall in blood pressure; acetylcholine and various anticholinesterases will accomplish much the same thing. However, in intact animals, after atropinization[35] and after curarization with d-tubocurarine or thiamine,[15] acetylcholine and prostigmine, respectively, cause a rise in blood pressure and an increase in heart rate; here then, acetylcholine exerts its nicotinic effects, undoubtedly on the sympathetic ganglia.

Another intriguing point is that atropine, usually considered to be an agent blocking the muscarinic effects of acetylcholine, may, in rather large doses, block skeletal muscle, and thus behave somewhat like curare.[10]

Several investigators have shown that acetylcholine may act as a stimulator in other ways. In heart-lung preparations of dogs and in isolated heart preparations of cats, guinea pigs and rabbits, Hoffmann and associates[36] show that acetylcholine after atropine produced epinephrine-like effects, which may be blocked by curare and ergotamine; the perfusate of such hearts contains an epinephrine-like substance. Middleton and others[37] show that an epinephrine-like substance may be obtained from the atropinized isolated cat heart on stimulation of the vagus; they interpret this finding to mean that adrenergic ganglia may be innervated by the vagus. Heymans and Bennati[38] suggest that in atropinized denervated hearts of adrenalectomized dogs, acetylcholine produces tachycardia, probably by stimulating intracardial sympathetic synapses.

The conclusion may be drawn that the vagus nerve contains fibers which, on stimulation, liberate sympathin, or which, when their synapses are stimulated by acetylcholine, liberate sympathin.

Burn and Vane[39] show that acetylcholine depresses the isolated rabbit heart, but after paludrine, may stimulate it. They theorize that acetylcholine is a material necessary for spontaneous contraction, and that its breakdown and formation produce rhythmic contraction. If acetylcholine is present in excess, the beat is stopped because the acetylcholine cannot be destroyed with sufficient speed. Paludrine depresses the heart, stops its rhythmic contraction, inferentially by reducing acetylcholine formation. Under these conditions, when acetylcholine is given, the beat is restored.

The obvious vagaries of the adrenergic endings include such vital questions as (a) What is the nature of sympathin E and sympathin I? (b) How does sympathin I act, that is, how can it produce an inhibition? (c) Most adrenergic blocking agents block only sympathin E or sympathin E effects *except those on the heart*[5]; what properties make the action of sympathin E on the heart unique in this fashion?

Another unusual response is reported by Bussell[40] who shows that constriction of vessels of the rabbit ear by epinephrine could be abolished by atropine. Atropine, in these experiments, plays the role of an adrenergic blocking agent! Similar results are reported by Burn and Dutta,[41] who show, in addition, that atropine and other materials can abolish the vasodilator action of epinephrine. These authors do not believe that vasoconstriction and vasodilation are due to epinephrine acting at different sites in a preparation as simple as the rabbit ear.

Mention of epinephrine introduces the interesting observations of Maddock and associates[42] who indicate that epinephrine, usually regarded as a mixture of adrenergic transmitters, may serve also as an anti-curare agent at the neuromuscular junction; this anticurare activity is abolished by dibenamine.

And the last vagary of autonomic activity to be discussed involves the pharmacology of the sweat glands. It is usually taught that the sweat glands in man are innervated by cholinergic sympathetic fibers, are therefore muscarinic, and are hence blocked by atropine and drugs which block the muscarinic action of acetylcholine.

Haimovici[43] points out that "cold sweat" in man cannot be suppressed by parasympatholytic drugs. He shows that profuse spontaneous sweating can be suppressed by dibenamine, as can sweating which results from injection of neosynephrine, but that mecholyl induced sweat-

ing even after dibenamine. In another paper,[44] Haimovici describes similar results on sweating produced by epinephrine and norepinephrine; these results suggest, he concludes, that sympathin E and the excitory component of epinephrine act synergistically with cholinergic stimulation in the production of sweat.

The vagaries of autonomic activity which I have enumerated include, as can be seen, two general types: those resulting from insufficient knowledge of the intimate physiology of the autonomic system (example: acetylcholine excitation of the heart, sweat gland innervation), and second, different action of a particular substance at two different sites (example: atropine and curare at nicotinic and at muscarinic endings).

To solve the first type of vagary it will be necessary to continue investigating the details of autonomic physiology, as is being done by so many ardent scientists.

To solve the second type of vagary, the investigator is being aided immeasurably by the production of new drugs whose chemical configuration is known. One might visualize any site in the autonomic system as a lock, which can be opened by a key in the form of a drug of the proper shape, or which might be closed (locked) by a blocking agent of the proper shape.

This popular field is being continually explored by many investigators. Pfeiffer[45] shows that for maximum muscarinic activity adjacent oxygen atoms must be at a distance of 5 and 7 Angstroms from one or more methyl groups attached to the quaternary nitrogen. The inhibitors of muscarinic activity have the same structure, but it is contained in a large "umbrella-like" molecule. Pfeiffer and associates[46] obtained two diatropines, and contrasted their curariform activity with their atropine analogues. Twinning the atropine through an amyl chain which separated the adjacent oxygens from the quaternary nitrogen by 7 Angstroms markedly enhanced their curariform activity.

Barlow and Ing[47] obtained compounds in which two quaternary ammonium groups were connected with carbon chains of various lengths. They conclude that the curariform activity of such compounds increases as the chain is lengthened to C_{10}, then decreases.

Nickerson and Gump[48] show that for adrenergic blocking activity, drugs must be a tertiary amine, or a quaternary derivative of a tertiary amine, have one beta-haloalkyl group capable of forming an ethylenimmonium derivative, must include an unsaturated ring substituent attached to the amine in only certain fashion, and there must be no substitution on the phenyl ring out of the plane of the ring.

Welsh[49] says that results of his work on the heart of the quahog, which is highly sensitive to acetylcholine, suggests "that the acetylcholine molecule, in reacting with what we have called the receptor substance, occupies an area having a special configuration, much as a piece of a jigsaw puzzle does." Any smaller molecule of the same proportions as acetylcholine may "help to complete the picture." Molecules not conforming to the shape of the acetylcholine molecule, cannot act as substitutes.

As students of medicine interested in research and the advancement of medical science, it would be well to realize that although a clear understanding of the generalities of autonomic function may be obtained, still many loose bits of knowledge lie about to be fitted into their logical place only through more complete understanding of autonomic function. These vagaries of autonomic function constitute many of the phases of research for the future.

REFERENCES

1. Nachmansohn, D. Biochem. Biophysica Acta, *4*:78, 1950.
2. Nachmansohn, D. Bull. Johns Hopkins Hosp., *83*:463, 1948.
3. Goodman, L., and Gilman, A. The Pharmacological Basis of Therapeutics, The Macmillan Company, New York, 1941.
4. Guyton, A. C., and Reeder, R. C J. Pharmacol. and Exper. Therap., *98*:188, 1950.
5. Nickerson, M. J. Pharmacol. and Exper. Therap., Part 11, *95*:27, 1949.
6. McIntyre, A. R. Curare. The University of Chicago Press, Chicago, 1947.
7. Dale, H. H., Feldberg, W. and Vogt, M. J. Physiol., *86*:353, 1936.

8. Brown, G. L., and Feldberg, W. J. Physiol., *86*:10P, 1936.
9. Acheson, G. H. Fed. Proc., *7*:447, 1948.
10. Luco, J. V., and Altamirano, M. Am. J. Physiol., *139*:520, 1943.
11. Luco, J. V., and Meza, J. Ciencia, *2*:298, 1941.
12. Luco, J. V., and Mesa, J. Rev. de med. y aliment., *5*:60, 1942-43.
13. Smith, J. A., Foa, P. P., Weinstein, H. R., Ludwig, A. S., and Wertheim, J. M. J. Pharmacol. and Exper. Therap., *93*:294, 1948.
14. Smith, J. A., Foa, P. P., and Weinstein, H. R. Science, *108*:412, 1948.
15. Smith, J. A., Post, M., and Zalman, S. Fed. Proc., *9*:117, 1950.
16. Craig, L. E. Chem. Rev., *42*:285, 1948.
17. Alam, M., Anrep, G. V., Barsoum, G. S., Talaat, M., and Weiniger, E. J. Physiol., *95*:148, 1939.
18. Rocha e Silva, M., and Schild, H. O. J. Physiol., *109*:448, 1949.
19. Grob, D., Lilienthal, Jr., J. L., and Harvey, A. M. Bull. Johns Hopkins Hosp., *80*:299, 1947.
20. Landmesser, C. M. Anesthesiology, *8*:506, 1947.
21. Foregger, R. J.A.M.A.,*142*:1344, 1950.
22. Smith, S. M., Brown, H. O., Toman, J. E. P., and Goodman, L. S. Anesthesiology, *8*:1, 1947.
23. Berry, R. G., and Forster, F. M. Fed. Proc., *7*:7, 1948.
24. Salama, S., and Wright, S. Brit. J. Pharmacol., *5*:49, 1950.
25. Minz, B., and Viel, K. Compt. rend. Soc. de biol., *140*:466, 1946.
26. Feitelberg, S., and Pick, E. P. Proc. Soc. Exper. Biol. Med., *49*:654, 1942.
27. McIntyre, A. R., Dunn, A. L., and Tullar, E. P. Fed. Proc., *5*:67, 1946.
28. McCawley, E. L. J. Pharmacol. Exper. Therap., *97*:129, 1949.
29. Moe, G. K., and Freyburger, W. A. J. Pharmacol. Exper. Therap., Part II, *98*:61, 1950.
30. Acheson, G. H., and Moe, G. K. J. Pharmacol. Exper. Therap., *87*:220, 1946.
31. Luco, J. V., and Marconi, J. J. Pharmacol. Exper. Therap., *95*:171, 1949.
32. Krayer, O., and Acheson, G. H. Physiol. Rev., *26*:383, 1946.
33. Eyzaguirre, C., Folk, B. P., Zierler, K. L., and Lilienthal, J. L., Jr. Am. J. Physiol., *155*:69, 1948.
34. Pardo, E. G., Rennick, B. R., and Moe, G. K. Am. J. Physiol., *161*:245, 1950.
35. Koppanyi, T. Bull. Johns Hopkins Hosp., *83*:532, 1948.
36. Hoffman, F., Hoffman, E. J., Middleton, S., and Talesnik, J. Am. J. Physiol., *144*:189, 1945.
37. Middleton, S., Middleton, H. H., and Toha, J. Am. J. Physiol., *158*:31, 1949.
38. Heymans, C., and Bennati, D. Arch. internat. de pharmacodyn. et de therap., *79*:486, 1949.
39. Burn, J. H., and Vane, J. R. J. Physiol., *108*:104, 1949.
40. Bussell, L. J. J. Pharmacol. Exper. Therap., *69*:128, 1940.
41. Burn, J. H., and Dutta, N. K. Brit. J. Pharmacol., *3*:354, 1948.
42. Maddock, W. O., Rankin, V. M., Youmans, W. B. Proc. Soc. Exper. Biol. Med., *67*:151, 1948.
43. Haimovici, H. Proc. Soc. Exper. Biol. Med., *68*:40, 1948.
44. Haimovici, H. Fed. Proc., *9*:54, 1950.
45. Pfeiffer, C. C. Science, *107*:94, 1948.
46. Kimura, K. K., Unna, K., and Pfeiffer, C. C. J. Pharmacol. Exper. Therap., *95*:149, 1949.
47. Barlow, R. B., and Ing, H. R. Nature, *161*:718, 1948.
48. Nickerson, M., and Gump, W. S. J. Pharmacol. Exper. Therap., *97*:25, 1949.
49. Welsh, J. H. American Scientist, *38*:239, 150.

ARTERIAL HYPERTENSION—

(*Continued from page* 6)

appearance of the malignant syndrome. With regard to the selection of patients for pyrogen therapy, in general, it appears that if renal excretory function is reduced by 50% or more, the response will be poor. This treatment must be regarded as experimental.

Conclusions

Cures of arterial hypertension are rarely achieved today, but much can be done to ameliorate the disease. The pathogenesis of hypertension remains unsolved but investigation is being pursued in the two principle theories, namely (1) the occurrence of circulating pressor agents, such as angiotonin; (2) the occurrence of increased vasomotor activity. Treatment must cover a wide variety of signs and symptoms because blood vessels are affected in most parts of the body. There are no highly specific remedies to lower the blood pressure but the discerning use of several agents leads to greater comfort for the patient, and in many cases to the prolongation of life.

CLINICAL-PATHOLOGIC CONFERENCE

From the Current Files of Mount Sinai Hospital, Chicago, Ill.

Chairman: DR. H. J. ISAACS

Case No. 2.

Dr. A. Goldman:

HISTORY. A 30 year old white female was admitted to Mount Sinai Hospital as a full term pregnancy on April 30, 1948. She gave a history of having had a heart murmur since the age of ten after a "cold" with a long convalescence. Since that time, she had not had any symptoms referable to the cardiovascular system such as ankle edema, dyspnea, orthopnea or palpitations.

Physical examination revealed a well developed, well nourished, pregnant white female about thirty years of age who was sitting up in bed without acute distress. Temperature was 97°, pulse 92, full and regular; respirations 30, and blood pressure 124/82. The lungs were clear to auscultation and percussion. The heart apex was palpated 8 cm. to the left of the midsternal line. There was enlargement of the heart in the 3rd left interspace giving a mital configuration. There was a harsh systolic murmur and a presystolic murmur at the apex. At Erb's point and in the aortic region a systolic murmur of a different pitch was heard which was transmitted over the entire base of the heart. A diagnosis of rheumatic heart disease with mitral stenosis, mitral regurgitation and aortic stenosis with no evidence of decompensation was made at this time. Other findings pertained to her pregnancy and were normal.

The patient was delivered of a 6½ pound baby boy. On the first postpartum day, the patient was somewhat dyspneic and physical examination revealed impaired resonance with suppression of breath sounds in the right lower lobe posteriorly. Temperature was normal. The patient responded to conservative treatment and digitoxin. She was discharged approximately ten days after admission with the diagnosis of right lower lobe pneumonia following pregnancy.

SECOND ADMISSION: The patient was readmitted to Mount Sinai Hospital on October 7, 1948, with the complaint of difficulty in breathing. This dyspnea had become progressively worse and included several paroxysmal nocturnal episodes. She also had had transient pedal edema and frequent episodes of fleeting precordial pain. In addition, she had developed a nonproductive cough one week prior to admission and stated that she had lost approximately twenty pounds since the onset of this illness.

Physical examination at this time revealed a well developed, poorly nourished white female about 30 years of age, who appeared to be in acute respiratory distress. The blood pressure was 110/80; pulse 120; respirations 34, labored and shallow. The skin was pale and moist. The jugular veins were engorged bilaterally and pulsated. Examination of the chest revealed limited excursions with dullness and absent tactile fremitus in both lung bases. There were decreased to absent breath sounds in both bases posteriorly. The apex impulse was palpated in the 5th and 6th interspaces in the anterior axillary line and a systolic thrill was palpable at both the apex and the aortic area. The systolic thrill at the apex was transmitted over the entire precordium while that of the aortic area was palpated in the neck. The heart rate was 130, and a systolic and a diastolic murmur were heard at the apex with a loud systolic murmur at the aortic area transmitted to the great vessels of the neck. The abdomen was soft. The liver edge was palpated three fingerbreadths below the costal margin and was tender. There was pitting edema of both extremities.

On the day following admission, a thoracentesis of the right chest was done and 1550 cc. of straw-colored fluid were removed. The patient was put on a cardiac diet, given mercuhydrin, digitalized and placed on penicillin (300,000 U.B.I.

D.) because of a low grade fever. The patient continued to run a low grade temperature and on frequent occasions a gallop-rhythm was noted. Thirteen days following admission, the patient passed bloody urine. The next day another thoracentesis yielded 1700 cc. of straw-colored fluid. The patient's condition did not change and streptomycin was added to her regime. On the 28th hospital day, 2600 cc. of fluid were removed by thoracentesis and 100,000 U. of penicillin were injected into the pleural cavity. The pulse remained rapid and the patient complained of nausea and weakness. Physical examination revealed the reformation of pleural fluid. She was taken off all medication and placed on salicylates. She felt better and appeared to improve for approximately one week until there was an elevation of temperature, tinnitus and vomiting. At this time the salicylate therapy had to be stopped and the patient again was placed on penicillin and streptomycin. On 11/17/49, the patient became very weak, her temperature began to spike and her pulse became rapid and weak. The following morning her pulse became imperceptible. There was marked dyspnea and the patient complained of severe back and abdominal pain. The apical rate was 140 and the B.P. was unobtainable. Despite plasma, desoxyn, digitalis and oxygen she expired at 10:40 A. M. on November 18, 1948, 43 days after her second admission.

LABORATORY FINDINGS

Blood Count	RBC	Hb.	Color Index	WBC	Stabs	Segs	Eos	Bas	Lymph	Mono.
10/29/47	3,610,000	67%	.94	7,850						
10/7/48	4,140,000	85%	1.03	10,800	3	84	2	1	7	3
10/20/48	4,120,000	81%	1.01	10,400		81		1	13	5
10/28/48				8,600	3	82	1		11	3
11/6/48	4,160,000	72%	.87	10,700	1	77	1	1	17	3
11/15/48	3,980,000	81%	1.03	7,300	1	71	2		16	10

Urinalysis	React.	Sp. Gr.	Alb.	Sugar	WBC	RBC	Casts
10/29/47	Acid	1.019	0	0	0	0	0
10/8/48	Acid	Q.N.S.	Tr.	0	20-25	0-2	0
10/18/48	Acid	1.016	Tr.	0	0	0-2	0
10/26/48	Acid	1.005	Tr.	0	15-20	0	
11/2/48	Acid	1.009	0	0	0-1	0	0
11/9/48	Acid	1.016	Ft. Tr.		1-5	0	
11/15/48	Acid	1.015	Tr.	0	25-30	5-10	
11/16/48	Acid	1.025	1+	0	25-30	75-100	0
11/17/48	Acid	Q.N.S.	3+	0	75-100	200-250	
11/18/48	Acid	1.020	2+	0	5-10	0-5	hyaline 3-8

Blood Chemistry	Sugar	Urea N.	Prot.	Alb.	Glob.	AG Ratio	Chlorides
10/8/48	102	11.1					
10/25/48		10.7	7.1	4.9	2.2	2.2/1	
10/28/48							578

Serology: Negative
Sed. Rates:
10/8/48 — 20 (N. 1-10)
10/30/48 — 27 "
11/6/48 — 35 "
11/15/48 — 38 "
Feces Analysis: Negative for blood.
Agglutination Tests: Negative

Blood Cultures: 10/15; 11/1; 11/3; 11/6 48—no growth

10/21/48 — Pathologic report: Thoracentesis fluid: Sp. Gr. 1.005. No cancer cells present.
11/13/48 — Blood Salicylate level: 77 mgm %.
11/17/48 — Blood Salicylate level: 0 mgm %.
10/29/48 — Prothrombin Time: 100% of Normal.
10/20/48 and 10/21/48 — Sputum: No acid-fast bacilli seen.

Dr. E. B. Freilich, Internist:

This 30 year old patient illustrates rheumatic heart disease in pregnancy. The history of rheumatic heart disease apparently goes back to the age of ten, and at the age of 26 she noticed some dyspnea on effort. She married, became pregnant and then some heart failure developed shortly after labor, with gradually increasing signs of heart failure, until she was finally admitted to the hospital. The findings were murmurs all over the heart, enlargement of the heart, hydrothorax, enlarged liver, and presence of low grade temperature which at that time was considered possibly due to infarction, to a fresh endocarditis, or to rheumatic pneumonitis. From the clinical point of view it is important that she did not let her husband know of her rheumatic heart disease at the time of marriage. In fact she refused to even be admitted to the hospital until she was in very bad condition because she did not want the family to know of her illness. In normal women, but particularly in cases of rheumatic heart disease, pregnancy results in a greater load on the heart. The increasing size of the uterus and fetus results in a greater blood volume, a greater cardiac output and greater demand for oxygen. She experienced some degree of heart failure shortly after labor, on account of the rheumatic involvement with serious damage to the heart. Following her discharge from the hospital, the care of the baby and doing her housework aggravated her condition, but the fact that she tried to keep her disease more or less secret from her family resulted in her refusal to be admitted to the hospital. I do not know whether it would have made any difference, but her medical treatment was certainly greatly delayed and when she finally came to the hospital she was practically in the terminal stage.

How should one manage pregnant women with rheumatic heart disease? As a rule, the greatest burden is thrown on the cardiovascular system around the fifth month of pregnancy. This continues until about 8½ months, when there seems to be a decrease of the load on the heart. Many obstetricians state that patients with rheumatic heart disease deliver comparatively easy, and tolerate the strain of labor fairly well. This holds true especially for multiparous women. Therapeutic abortion is indicated when heart failure occurs prior to the pregnancy. Aortic involvement is of much more serious significance, and there is a definite indication in the case of auricular fibrillation. Both the obstetrician and the internist are also faced with the problem whether to permit the woman to go through normal labor or whether to do cesarean section. Some time ago cesarean section was favored because of the lessened work on the heart, but at least cesarean sections are done much less frequently because operative sequelae may occur, particularly pulmonary atelectasis, and make a decision for cesarean section rather difficult.

Dr. H. N. Kamin, Cardiologist:

The electrocardiogram showed QRS_1 and QRS_2 to be biphasic. QRS_3 was upright. The precordial leads showed an inverted QRS_1. In leads CF_4 and CF_5, the QRS was upright. These findings are compatible with left and right heart strain.

I saw the patient during her hospital stay, and thus could appreciate the many problems involved. First we assumed that it was a simple case of rheumatic heart disease with cardiac failure and hydrothorax. After a few days observation we realized that we were dealing with more than that because the temperature persisted, the pleural fluid refilled very rapidly, and clotted, indicating presence of abundant fibrin. Therefore we began to wonder whether we were dealing with an additional pneumonic process, perhaps a similar condition as was shown in the first patient. X-ray showed some pneumonic infiltration. The laboratory tests were all negative. We finally decided that we were dealing with some form of pneumonitis with pleuritis. This would explain the rapid fibrillation and the temperature. We also postulated recurrent rheumatic fever, involving both the heart in the form of carditis, and the lungs in the form of pleuritis. Later the patient showed some red and white cells in the urine and we also considered kid-

ney involvement of rheumatic etiology. Another problem was the severe backache and abdominal pain on the day before expiration. We considered at that time mesenteric thrombosis, possibly on the basis of some vascular injury, as may occur in rheumatic fever.

Dr. H. J. Yellen:

At the time of her death, it was my impression that she had an extremely huge left auricle. Possibly there was an intraauricular thrombus, and the cause of death may have been due to the thrombus being partially dislodged and being pressed down into the opening of the mitral valve.

Dr. J. Arendt, Radiologist:

Our films showed an enlarged heart shadow, the right border obscured by a homogeneous density, which also covered the right diaphragm. The heart demonstrated a characteristic deformity which even without an esophagram indicated a left auricular enlargement and the presence of a mitral stenosis. On consecutive films we found more and more the left sided prominence of the left auricle and its appendage. This is in our opinion quite characteristic of an intraauricular thrombus in the left auricle. We have as yet not succeeded in demonstrating such noncalcified thrombi in the right auricle. With such a degree of auricular distension we usually have evidence of auricular fibrillation. The density in the right base of the lung was very likely an infarct accompanied by pleurisy. There was some moderate congestion over both lungs.

Dr. A. F. Lash, Obstetrician:

From the obstetrical point of view, we are always concerned when we find evidence of mitral lesions because they represent a serious complication in obstetrics. We do not think that pregnancy itself plays so much of a part in bringing about decompensation. The second stage of labor probably has a definite deleterious effect upon the cardiac condition. However, the time when we are especially concerned about the cardiac pathology is immediately after delivery and during the puerperium. Immediately after delivery there is a drop of the diaphragm, expansion of the lungs, and thus there results a marked change in respiratory-cardiovascular relationship. As a result of this I have several times seen rheumatic patients go into acute cardiac failure. Later during puerperium, like in this patient, cardiac failure may be the result of getting up at night to take care of the baby and working throughout the day with very little rest periods. Therefore, when deciding on whether or not a woman with cardiac pathology should be permitted to have a baby we must consider her social condition in addition to her physical condition. In patients with rheumatic heart disease the obstetrician should always insist on consultation with the cardiologist. In general, if a patient with mitral stenosis has never had any previous episode of decompensation, we might allow her to have one child and feel perfectly justified in sterilizing her after that one child. If she gave birth to one child, we view another pregnancy with a great deal of apprehension, because rarely do we see any of these patients have more than one child without any serious consequence. We feel that the most important therapy during pregnancy is rest. If there is any drug that seems to help them in particular, the drug is morphine.

Dr. M. Kirschen, Internist:

I would like to touch on only one point. Originally we always used to think about the difficulties of a cardiac patient in pregnancy and after pregnancy in terms of mechanical difficulties, which affect the heart during these periods. We also paid attentiton to the problem of taking care of the child which increased the strain on the heart. Although those factors hold true to full extent, I believe that we will have to reevaluate them. According to reports in the literature which accumulate to an increasing degree, the factor which is most detrimental and which determines the course of a patient with rheumatic heart is the not so infrequent reactivation of the rheumatic process. This may often remain unnoticed and particularly in the last few months of pregnancy the reactivation in the form of a mild endocarditis may escape detection. For this reason, patients with old rheumatic heart disease who are dis-

charged after delivery should be very carefully watched for the first months in order not to miss the above mentioned complications.

Dr. H. Hirschfield, Resident:

It may be important to point out that towards the end we took the patient off all her medications and placed her on salicylates. The medication started with 60 grains and was built up to 75 grains per day. After about one week on this therapy she became nauseated, vomited, developed tinnitus and laboratory reports indicated progressive hematuria, both gross and microscopic. On the day after the symptoms developed, the salicylate blood level was found to be 77 mg. per 100 cc. The salicylate medication was stopped for a day or two but the hematuria still increased and only disappeared shortly before expiration of the patient. I believe Coburn has suggested to give at least one grain per Kg. of body weight and even doses of 200 grains per day. In this patient a dose which was below that recommended in the literature resulted in a high salicylate level with evidence of toxicity and hematuria.

Dr. I. Davidsohn, Pathologist:

The interesting feature of this case is that it makes it possible for us to compare it with the previously reported case. Both patients had rheumatic fever complicated by pregnancy.

AUTOPSY. The heart weighed 683 Gm., more than twice the normal weight. There was adhesive pericarditis with obliteration of the pericardial sac. The left atrium was markedly dilated and the wall hypertrophied. The mital valve was deformed, showing the so-called fish-mouth type, with resulting stenosis of the ostium (Fig. 3). There was no evidence of acute lesions. In the left auricular appendage there was a fairly small thrombus, protruding into the lumen of the auricle. There was no ball thrombus present and, therefore, no possibility for occlusion of the ostium. The chordae tendineae were fibrosed, the wall of the left ventricle was hypertrophied. The cusps of the aortic valve were shortened, thickened and calcified with resulting extreme narrowing of the ostium, typical aortic stenosis and insufficiency, the stenosis much in the foreground (Fig. 4). There was an endocardial pocket below the level of the aortic valve on the left ventricular side of the interventricular septum. The microscopic sections showed no Aschoff nodules. In the subepicardial fat small arteries with thick hyperplastic hypertrophied walls were present of the type frequently referred to as post-rheumatic.

The other organs showed extreme chronic passive congestion. The liver weighed 1400 Gm. Sections showed central necrosis, resulting from acute heart failure.

The lungs weighed only about 30 per cent above the normal, which is a striking contrast when compared with the lungs of the preceding patient where the weight was about three times the normal. The increase in weight in this case was very insignificant, especially in view of the fact that there were foci of acute bronchopneumonia. There was no evidence of any lesions similar to those described in the previous case. There was some atelectasis due to compression by the fluid, and areas of terminal bronchopneumonia.

Anatomic and Microscopic Diagnosis

HEART: Concentric hypertrophy; old fibroplastic (rheumatic) deformity of mitral valve resulting in severe stenosis of mitral ostium and insufficiency of mitral valve; calcareous old fibroplastic (rheumatic) deformity of aortic valve resulting in marked stenosis of aortic ostium and moderate insufficiency of aortic valve; adhesive pericarditis; stenosis of right coronary ostium; fibrosis of myocardium; mural thrombi in left auricular appendage; subepicardial hemorrhages.

LUNGS: Hydrothorax, bilateral; chronic passive congestion; focal atelectasis; terminal bronchopneumonia.

LIVER: Acute passive congestion; focal or central necrosis. KIDNEYS, SPLEEN, URINARY BLADDER, UTERUS: Acute passive congestion. OVARIES: Follicle cysts.

It is interesting that in spite of the similar background, as expressed in the presence of the rheumatic process, apparently extending over a long time, and of the complicating pregnancy, the changes

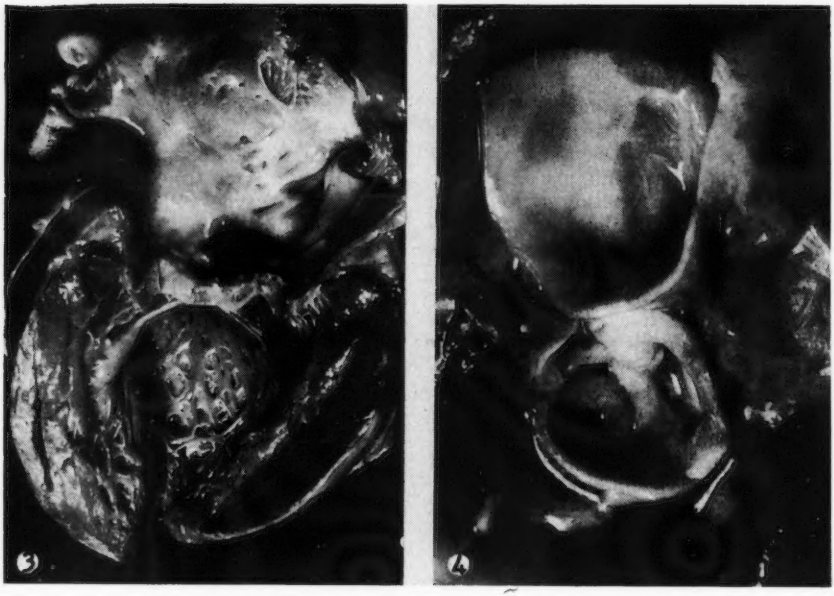


Fig. 3. Heart. Left ventricle. The outstanding features are the considerable hypertrophy of the left ventricle, the hypertrophy and distention of the left auricle, and the severe old rheumatic changes in the mitral valve.

Fig. 4. This is a view of the aortic ostium as seen from above, that is looking from the aorta into the left ventricle. The severe deformity of the aortic valve has led to an extreme narrowing of the ostium.

are entirely dissimilar in the two cases presented today. One cannot make any suggestions why the changes in one patient were of one type and of an entirely different type in the other patient. It is obvious that in addition to the exogenous factors, one has to introduce endogenous factors. Dr. Stern, with whom I discussed this subject, made a good suggestion. If the endogenous factors are of the nature of constitutional characteristics, then it is reasonable to assume that they are dependent on genes. It has been estimated that in mice there are about 10,000 different and distinct genes. In inbred strains of mice the similarity of individual mice is based on the identity of not more than 75 per cent of the genes. Man has probably a larger number of genes. Therefore, it is quite apparent that it is difficult to evaluate the role of endogenous constitutional factors, and still more difficult to draw conclusions.

The question regarding the relation between pregnancy and reactivation of the rheumatic process is difficult to answer in a short time if at all. It is apparent that two possibilities have to be considered: (1) reactivation of the rheumatic process brought about by pregnancy, and (2) the added burden on the heart resulting from mechanical factors in the pregnancy. It is possible that both of them may be involved in different cases. Certainly, in the second case, with no anatomic evidence of reactivation, this factor was not operative.

CURRENT COMMENT

The General Adaptation Syndrome and Diseases of Adaptation

HUGO R. RONY, M.D.*

Since their introduction by Hans Selye in the medical literature four years ago (1) the above terms and the underlying conceptions have received widespread interest and considerable approval and application. The term "general adaptation syndrome" is a physiological concept attempting to integrate earlier observations and some important recent experimental data — the latter contributed mainly by Selye and his collaborators — into a general thesis of adaptation to stress. The merit of this concept is that it enables us to recognize order, i.e., cause and effect in an otherwise chaotic mass of data. Furthermore, on the basis of this physiological concept certain important pathological conditions are assumed to be due to abnormal adaptive reactions; and these assumptions may open up new approaches to the pathogenesis of some diseases.

The General Adaptation Syndrome

The knowledge that living organisms are capable of adapting themselves to environmental as well as internal changes is not new — as a matter of fact, it had been long recognized that this capacity is one of the main characteristics of living matter. Many adaptive reactions had been described in response to *specific* harms, such as the sudden outpour of adrenalin in fright and other emergencies, or the immune reactions to bacterial and other antigens; and various so-called homeostatic mechanisms had been discovered that rectify alterations in the internal equilibrium, such as the mechanisms regulating body temperature, blood sugar, etc. These adaptive responses are more or less specific in that a certain kind of response is elicited by a certain type of stimulus. Now, according to Selye, it is important to recognize that — aside from or in addition to such specific adaptive reactions — a definite series of adaptive reactions occur in response to any kind of major stress irrespective of the specific nature of the stress. The sum of these non-specific morphological and functional reactions is termed the *general* adaptation syndrome. Selye asserts that the most important reactions are related to the adrenal cortex: the cortex shows enlargement and signs of increased activity; its secretion of corticoid hormones increases; as a result involution of the lymphatic apparatus and certain metabolic changes develop leading to changes in the specific and general resistance of the organism.

In response to continued exposure to stress the adaptive reactions follow a definite pattern of subsequent stages, according to Selye.

1) "The alarm reaction" in which two phases can be recognized: The "shock" phase represents signs of damage manifested by hypothermia, hypotension, hemoconcentration, low BMR, hypochloremia, hyponatronemia, hyperpotassemia, hyperglycemia followed by low blood sugar, excess tissue katabolism with increased NPN and PO_4 in the blood, leukocytosis, bleeding gastro-intestinal ulcers and depression of the nervous system. Selye calls attention to the fact that most of these changes occur in adrenal insufficiency and suggests, on this basis, that in the shock phase a "relative" adrenal insufficiency exists. Then the "countershock" phase sets in with its manifestations of defense: body temperature, blood pressure, basal metabolic rate, blood sugar, chloride and sodium rise to normal.

2) If exposure to the stress continues the phases of the alarm reaction are followed by the "stage of resistance" in which further signs of adaptation become manifest. These include involution of the thymus and lymph glands, lymphopenia in the blood and increase in the serum globulin content at the expense of serum albumin. At the same time the animal shows increased specific resistance in that the same stress repeatedly applied can no longer elicit the signs of "shock" (while resistance to other types of stress is frequently decreased). Fur-

* Associate Professor of Clinical Medicine, The Chicago Medical School.

thermore, in this stage under certain conditions — in unilaterally nephrectomized animals kept on high protein, high sodium diet — hypertension, periarteritis nodosa, hyalinization and inflammation of the renal arterioles and formation of fibrous nodules in the heart resembling Aschoff bodies develop. Since these changes in the counter-shock and resistance periods are accompanied by adrenal cortical hypertrophy, and are entirely missed in hypophysectomized or adrenalectomized animals exposed to the same stress, Selye believes that they are caused by excess production of adrenal corticoid hormones in response to excess corticotrophin secretion by the anterior hypophysis.

3) Upon further exposure to severe stress the stage of resistance is followed by "the stage of exhaustion" representing failure of the adaptive mechanism; blood sugar, chloride and sodium decrease, blood potassium increases, resistance to the same stress declines. This is attributed to exhaustion of the adrenal cortex resulting in diminished production of corticoids.

Considerable caution is exercised by Selye concerning the pathways through which the adaptive mechanism operates. He suggests that in the first phase of the alarm reaction sympathetic nerve centers in the hypothalamus are stimulated from the area of stress in some unidentified humoral or nervous way. This leads to liberation of excess sympathin at hepatic nerve endings as well as to excess adrenalin production in the adrenal medulla, resulting in immediate release of free glucose into the blood from hepatic glycogen reserves. As the stress continues, the anterior hypophysis is stimulated — again through unidentified pathways — to produce excess adrenocorticotrophin which, in turn, results in excess secretion of adrenal corticoids. The secretion of gluco-corticoids as well as mineralo-corticoids is increased although the ratio may vary depending on the animal species, individual constitution, on the kind, severity and duration of the stress, and on the diet and other experimental conditions. Both types of corticoids contribute to the development of resistance. The gluco-corticoids — such as Compound E — promote glycogen formation from protein and the "transposition of protein" essential for regeneration; also they promote liberation of gamma-globulin from lymphocytes which facilitates cellular and serological defense. The mineralo-corticoids—such as desoxycorticosterone — are essential for resistance in that they act to restore electrolyte equilibrium that had been deranged in the shock phase.

Diseases of Adaptation in Man

Addison's disease with its characteristic lack of defense against any kind of stress may be regarded, according to Selye, as a primary failure of the adaptive mechanism. The *Waterhouse-Friderichsen syndrome* represents a particulary severe alarm reaction: "grave intoxication with microbial products calls for an enormous increase of corticoids, a state of relative adrenal insufficiency is created with eventual breakdown of the hyperactive adrenal." *Acute gastro-intestinal ulcers* occurring after extensive burns or in acute infections may be due to insufficiency of the adaptive mechanism; possibly, such pathogenesis might be valid for chronic peptic ulcers.

Other pathological conditions may arise in connection with excessive or abnormal adaptive reactions. Among such diseases — hitherto regarded as "idiopathic" — Selye lists *essential hypertension, periarteritis nodosa, nephrosclerosis, nephritis, rheumatic diseases* and, possibly, *eclampsia* and certain forms of *tonsillitis* and *appendicitis*. It is assumed that in these diseases excess corticoid production is elicited and maintained by continued stress; while *Cushing's disease* may be regarded as a primary form of excess corticoid production. As the main support for these assertions Selye cites the fact that under certain conditions similar pathological states can be produced in experimental animals by the administration of pituitary corticotrophin or adrenal corticoids.

Discussion

The term "general adaptation syndrome" is somewhat confusing in view of the fact that the syndrome necessarily includes the initial shock phase which represents damage when effective adap-

tive reactions have not yet developed. For this reason it would seem to be more correct to call the syndrome "the general stress syndrome" consisting of a phase of shock or damage and subsequent phases of adaptive reactions.

Some elements of the theory of adaptation are more or less speculative or hypothetical and may have to be revised in the future without materially altering the validity of the theory as a whole. The main contention — that recovery in stress requires excess production of adrenal corticoids — seems to be well established even though direct evidence by way of hormonal assay in the blood or urine is not yet available. Some of the indirect proofs are quite impressive:

1) Enlargement of the adrenal cortex due to individual cell hypertrophy with discharge of lipid granules — regarded as a sign of increased cortical activity — is pronounced in practically all kinds of stress that has been investigated. These include exposure to low temperatures, burns, hemorrhage, X-ray irradiation, infections, fasting, toxins, drugs, anoxia, severe muscular exercise, nervous stress.

2) Rapid decrease of the cholesterol content of the adrenal cortex — a known sign of increased cortical activity — has been regularly demonstrated in experimental animals exposed to various alarm stimuli.

3) Involution of the thymus and lymph glands with lymphopenia in the blood — known to be an effect of excess glucocorticoids — is a constant feature of the alarm reaction. Moreover, these changes do not develop in hypophysectomized or adrenalectomized rats exposed to the same stress, and here the shock phase is particularly severe and the countershock phase negligible or absent.

4) Administration of adrenal corticoids can prevent shock in normal rats. In view of these and other minor evidences the general role of the adrenal cortex in the physiology of adaptation to stress is now generally recognized.

No objection can be raised against listing Addison's disease, the Waterhouse-Friderichsen syndrome and Cushing's syndrome as "Diseases of Adaptation." However, nothing new or particularly instructive is added to the pathogenesis by this classification, as the lack of defense in stress in the two first named diseases, and the role of the adrenal cortex in all three had long been recognized.

On the other hand, classifying hypertension, periarteritis nodosa, nephrosclerosis, nephritis and the rheumatic diseases as diseases of adaptation means not merely a new terminology; it involves important new pathogenetic conceptions. Selye suggests that in all, or at least in certain forms of these diseases, a) the pathological process is initiated by continued exposure to stress, b) in response to the stress excessive or abnormal corticoid — especially mineralocorticoid — production takes place leading to endogenous intoxication with the subject's own corticoids, and c) corticoid intoxication induces the specific pathological processes, the kind of tissue and type of change depending on inherited disposition, diet and other individual factors. As mentioned above, Selye has shown that more or less similar pathological pictures can be observed under certain conditions in rats exposed to continued stress, and can be produced by administration of large amounts of synthetic mineralo-corticoids, e.g., desoxycorticosterone in that species. But as yet no evidence had been offered to show that increased mineralo-corticoid production actually exists in these diseases of man: the adrenal cortex shows no hypertrophy, the known effects of mineralocorticoids on the electrolyte equilibrium are absent, and reliable assays of the corticoids in the blood or urine are not available. (It is true that one of these pathological conditions, hypertension, commonly occurs in Cushing's disease due to adreno-cortical tumor or hyperplasia; but in Cushing's disease an "unbalanced" gluco-corticoid, rather than mineralocorticoid, excess is believed to exist.) Hence, the conception that the diseases listed in this paragraph represent diseases of adaptation remains entirely speculative—at best, a working hypothesis.

BIBLIOGRAPHY

1. Selye, H.: The general adaptation syndrome and diseases of adaptation. J. Clin. Endocrinology *6:* 117, 1946.
.—Text of Endocrinology, 4th ed., 837, 1948.

BOOK REVIEWS

RESEARCH IN MEDICAL SCIENCE. Edited by David E. Green, Ph.D., and W. Eugene Knox, M.D. Cloth. 492 pages. New York: Macmillan Company, 1950. $6.50.

For some time, a need has been felt for a work which would cover the research done in the basic sciences and which would be intelligible to the average medical student and practitioner. Without question, Dr. Green's and Dr. Knox's collection of essays is the finest work of its kind to be published in recent times.

Rather than present original papers, the editors have invited the foremost research men in the individual fields to write an essay embodying the recent work done in his specialty and indicating, if possible, the avenues of research that are presenting themselves for future progress. Covering such varied topics as Hypertension, Liver Injury, Chemotherapy, Aspects of Red Cell Production, Endocrinology in Cancer Research and many others, it is comprehensive enough to interest all of its readers. The complete bibliographies at the end of each chapter are representative of the literature of that field and will guide the interested student in his further readings in that particular subject. Its nontechnical presentation and clear, precise writing make it possible for the reader to retain the essential points without having to digest a mass of formulas and mathematical equations.

It is only via such books that the student — and practitioner — will become aware of the progress that is going on in the research in the basic sciences. A book such as this is not only informative; it is stimulating as well. As the editors say, "The medical student should come away with a more realistic appreciation of what it takes to embark upon a career of medical research. The clinician should recognize his close dependance upon many fundamental disciplines if he is to pursue his investigations and practice to the greatest advantage. The chemist should realize that there is a great gap between fundamentals on the one hand and disease processes on the other; and that if he is to make his proper contribution, he must be ready to acquire a more than superficial understanding of biochemistry."

The book is highly recommended to the medical student and should be in the medical library of all physicians.

A TEXTBOOK OF BIOCHEMISTRY by Benjamin Harrow, Ph.D. Fifth Edition. Cloth. 609 pages. Philadelphia and London: 1950. $6.00.

After four years, this newly revised Textbook of Biochemistry fills a need which has long been apparent. Long a standard in its field, it presents the compactness, accuracy and legibility of the previous issues. In addition to an extensive revision including such topics as paper chromatography, shock, histamine and antihistamine reagents, hormones and carcinogenesis, protein inhibitors, alcaptonuria, muscle contraction, therapeutic uses of estrogens and androgens and diisopropylfluorophosphate (DFP), the chapter on chemical respiration has been completely rewritten and a new chapter on Biological Antagonists has been added. The book is highly recommended to medical students and should be in the library of all practitioners who want to renew their fundamental knowledge of the chemical background of the practice of medicine.

THE PRACTICE OF REFRACTION by Sir Stewart Duke-Elder. K.C.V.O., M.A., D.Sc., Ph.D., M.D., F.R.C S., Hond. D.Sc. Fifth Edition. Cloth. 317 Pages with 216 illustrations. St. Louis: C. V. Mosby Co., 1949. $4.50.

With the aim of this volume being to instruct both the student and practitioner in "the essential principles of the theory and practice of the correction of defects in the optical system of the eyes and their associated muscles" it necessarily covers a large amount of material. It has been extensively revised since the last edition, and the presentation, although technical, can be easily understood by those with a background of one year of college physics and the standard medical school course in optical physiology. The techniques described are easily followed and the equipment described is modern. This book is recommended to all senior medical students and practitioners and should be in the medical library of all oculists.

MENSTRUATION AND ITS DISORDERS. Edited by Earl T. Engle. Cloth. 358 Pages. Springfield, Illinois: Charles C. Thomas, 1950. $6.50.

This book presents the proceedings of the annual conference of the National Committee on Maternal Health which dealt with one aspect of human fertility—menstruation. The most modern concepts of the physiology and functional pathology of the menstrual cycle and menstruation are discussed by several of the leading scientists and clinicians in the field of experimental and clinical gynecology. The many recent developments in the sphere of the chemical, enzymatic and other metabolic processes within the endometrium are well described by the various investigators. The illustrations and charts are well chosen and contribute to a clearer understanding of the textual material. The print and binding are excellent. The book is highly recommended to all students and practitioners engaged in the study of didactic as well as clinical obstetrics and gynecology.

CORRECTION

Page 124 of Volume II (July, 1950), Laboratory Findings, No. 3, Cephalin Cholesterol Flocculation, should read, "which is common in surgical jaundice, jaundice produced by drugs and toxins and the idiopathic group."

SCHOOL NOTES AND NEWS

FACULTY NEWS

It is with great pride that we welcome to the faculty of the Chicago Medical School, Dr. Herman Josephy as Associate Professor in Neurology. Dr. Josephy brings with him a wealth of teaching and clinical experience.

Dr. Josephy, born in 1810, was brought up in Germany where he received his degree of Doctor of Medicine in 1910. After completing his internship, he was appointed physician at the Mental Hospital (University Hospital) of the Univerity of Hamburg. He continued at this position from 1914 to 1930. During this period of time, he was appointed Associate Professor of Neurology at the University of Hamburg from 1924 to 1933. In 1930, Dr. Josephy was appointed Director of the Neuropathological Laboratories at the Mental Hospital. In 1933, Dr. Josephy left Germany.

Besides being certified by the American Board in Psychiatry and Neurology and the American Board in Pathological Anatomy, Dr. Josephy is the Attending Neuropathologist at the Chicago State Hospital and a member of the American Medical Association, American Association of Neuropathologists, American Academy for Cerebral Palsy, Fellow of the American Academy of Neurology, Chicago Pathological Society, and the Chicago Neurological Society.

Dr. Josephy has published about 50 papers mainly in the field of neuropathology. Among his works are the "Handbuch der Inneren Sekretion," "Handbuch der Geisteskrankheiten," and the "Handbuch der Neurologie."

Dr. Herman Josephy

Dr. Harold Elishewitz

We would like to take this opportunity to welcome Dr. Harold Elishewitz to the preclinical staff as Assistant Professor of Parasitology of the Department of Microbiology and Public Health of The Chicago Medical School.

Dr. Elishewitz, born in New York City in 1918, received his Bachelor of Science degree from Cornell in 1938. He was then awarded a research fellowship in bacteriology at the University of Rochester, School of Medicine and Dentistry for the period of 1938-39. He then entered the Graduate School of Harvard University where he received his Master of Science degree in 1940. Upon completion of his studies in the field of Parasitology at the University of Minnesota, he was awarded his Doctor of Philosophy degree in 1942.

It was at this time that Dr. Elishewitz was appointed Chairman of the Section of Parasitology of the Naval Medical Research Institute at Bethesda, Maryland. In 1943, he entered the Research and Development branch of the Quartermaster General Military Planning Division at Washington, D.C. During this period, Dr. Elishewitz was Secretary of the National Research Council of the O.S.R.D. Committee on Insectides. From 1944 to 1945 Dr. Elishewitz was associated with the Pan-American Sanitary Bureau at Guatemala and Southern Mexico where he worked on the problem of Onchocercosis. Upon completion of this project, he entered the services of the Standard Oil Co. (N.J.) Medical Deparment. In the following two-year period, Dr. Elishewitz traveled throughout South America and the Carribeans doing parasitological and medical-entomological surveys. In 1947, he became a consultant parasitologist for the various oil companies in South America and continued the aforementioned surveys. In 1950, Dr. Elishewitz returned to America and was appointed Assistant Professor of Parasitology at The Chicago Medical School.

Dr. Elishewitz is a member of the American Chemical Society, American Association for the Advancement of Science, Entomological Society of America, American Society of Parasitologists, American Society of Tropical Medicine, American Society of Protozoologists, Royal Society of Tropical Medicine, Inter-American Society of Sanitary Engineers, and many other American and South American societies in these fields.

Department of Microbiology and Public Health

Dr. H. Elishewitz has been appointed as Chairman of the Committee on the Clearing of Information relative to the cultures of parasites for the Midwest Parasitology Society meeting at Lansing, Michigan.

New Staff Appointments

Dr. Morris D. Bennin (Alumnus) ....
.....Assistant in Ophthalmology

Dr. Jacob S. Fishman .....Associate in the Department of Medicine

Dr. Milton M. Kadin .....
.....Assistant in Medicine

Dr. Irene Scheff has been appointed to the faculty of The Chicago Medical School as Research Associate. Dr. Scheff is a graduate of the University of Zurich, Switzerland, and of the University of Pecs, Hungary. She will be working under a grant of $6,200.00 awarded to the School by the Chicago Heart Association to be used for a research project having to do with the nature of the blood vessels of the capillary system.

SCHOOL NEWS

"At the present this region (9th Region) of the Civil Aeronautics Administration has vacancies for Medical Officers to be located with our organizations on Wake Island and Canton Island. Persons appointed to these positions at Canton and Wake Islands will be under the supervision of Philip M. Corboy, M. D., Regional Medical Officer for the CAA in Honolulu. Dr. Corboy attained his B. S. degree from Loyola University in 1928 and his M. D. from Loyola University, College of Medicine in 1932.

Individuals who meet the requirements and are interested in obtaining more information relative to these vacancies should contact Assistant Dean, Dr. Andrew H. Ryan. Further information can also be obtained from the Civil Aeronautics Administration, P. O. Box No. 4009, Honolulu, T.H., attention of the Personnel Office."

Four new research grants amounting to $15,365.00 have been received by The Chicago Medical School. One grant of $14,000 has been awarded by the U. S. Public Health Service upon recommen-

dation of the National Heart Institute for the extension of the teaching program of Cardiology at the School. Another grant of $825.00 has been received from the Committee for Research in Problems of Sex of the National Research Council, to be used for studies on sex behavior. A grant of $440.00 from the Veterans Administration will be used for research work having to do with the nerve endings in the gums and teeth. The final grant of $100.00 from the Chelcolt Laboratories has been awarded to Dr. Jay A. Smith for the purchase of equipment for use in studies of metabolism.

STUDENT NEWS

Class of 1952

Abraham E. Goldminz of 5501 14th Avenue, Brooklyn, has been awarded the Board of Trustees Scholarship for the highest academic standing among sophomore students at The Chicago Medical School in the past year.

Mr. Goldminz, the son of Mr. and Mrs. Joseph Goldminz, is a graduate of the New Utrecht High School and of the College of the City of New York.

ALUMNI

The Alumni Association extends its heartfelt sympathy to the family and friends of these honored dead:

Dr. Peter J. Latz of Chicago, Illinois, Class of 1899.

Dr. Irving Ginsburg of Chicago, Illinois, Class of 1938

Dr. Nunzio T. Cerasa of Peru, Illinois, Class of 1946.

Class of 1925

Dr. August F. Daro has been elected Alternate Councilor of the Northwest Medical Society.

Class of 1927

Dr. Joseph F. O'Malley has been elected President of the West Side Medical Society.

Class of 1928

Dr. Caesar Portes has been elected President of the International Academy of Proctology at their meeting in San Francisco. Dr. Portes has also been elected Councilor of the North Side Medical Society.

Class of 1937

Dr. Harry C. Leavitt of Seattle, Wash., has been certified by the American Board of Psychiatry and Neurology (Psychiatry) in June 1950.

Class of 1941

Dr. Arnold S. Block announces the opening of his office for the practice of Psychiatry in St. Louis, Missouri. Dr. Block is a Diplomate of the American Board of Psychiatry and Neurology.

Class of 1943

Dr. and Mrs. Abraham Rottkov of Ashokan, N. Y., announce the birth of their daughter, Linda Francine on July 22, 1950.

Class of 1944

Dr. Robert E. Bodwin has been elected Alternate Councilor of the North Shore Medical Society.

Class of 1947

Dr. Bernard Bloom announces the opening of his office at Woodridge, New York for the practice of Medicine and Surgery.

Class of 1950

Congratulations to Dr. and Mrs. Irwin Morse on the announcement of the birth of their son, Marc Saulley Morse on July 19, 1950.

STUDENT COUNCIL ACTIVITIES

In October 1949 a Student Council was formed and a constitution ratified by the student body.

The aims of the organization are clearly defined in the preamble to the constitution, which is as follows:

"1. In order to coordinate student activities;

2. To create closer relationships between the students, faculty, administration, and student organizations;

3. To aid our fellow students;

4. To be of all possible assistance in helping to develop and maintain the high standards of medical education and investigative work;

5. To enhance the reputation of our medical school and its graduates and society in general and the profession specifically;

We therefore form this Student Council.

Representatives to the Council are elected annually by the four classes and all accredited student organizations and fraternities. Officers are elected by these representatives. The present officers are:

President.....Leonard Gordon '50
Vice President.....Melvin Eisenberg '51
Financial Secretary..Walter Charles '51
Secretary.....Walter Kitt '52
Faculty Advisor.....Dr. Donald Atlas

In accordance with the principles of the preamble enumerated above, the following achievements were accomplished:

1. Establishment of a "Maurice Oppenheim Memorial Student Loan Fund" financially supported by contributions of the student body.
2. Establishment of an annual internship survey questionnaire.
3. Establishment of an official school key for graduating seniors.
4. Establishment of a school directory.
5. Establishment of a housing committee and orientation program set up to aid the incoming freshmen.

Dates for Student Council meetings are posted on the bulletin boards. The student and faculty are welcome and encouraged to participate in the proceedings.

We would like to take this opportunity to thank the administration and student body for the cooperation we have received.

ORGANIZATIONS

Phi Lambda Kappa

Alpha Rho Chapter of Phi Lambda Kappa is all set to swing into action after a relatively active summer which found most of the Juniors frolicking at their respective homes during the last three months. The fall program is being arranged to present to members, both new and old, a series of smokers, dances and educational lectures. The latter is to be featured by the appearance of Dr. Karl Menninger at the second annual Maurice Oppenheim lectureship which was inaugurated so successfully by Dr. Page last year.

This year the fraternity will be again pleased to sponsor a series of medical educational films to be shown at the school. The education committee is at present hard at work digging out movies that will prove to be interesting and informative to all students.

Since the very successful dinner dance in May many of our seniors have left the fold of Alpha Rho chapter and are busy at work interning. Those members in Chicago for the summer managed to have a beach party during the month of August and a good time was had by all.

Phi Delta Epsilon

The first annual lectureship established in honor of Dr. John J. Sheinin by the Beta Tau Chapter of Phi Delta Epsilon will be held in the Kling Auditorium of Mt. Sinai Hospital on October 16, at 7:30 P.M.

Dr. Robert E. Gross, Surgeon-in-Chief of the Boston Children's Hospital, will speak on the subject of "Neoplasms in Infancy and Childhood." Dr. Gross is also William E. Ladd Professor of Children's Surgery at Harvard Medical School.

Dr. Gross will deliver two other lectures for Phi Delta Epsilon chapters at Northwestrn University and the University of Illinois. A dinner in his honor will be held at the Standard Club, sponsored by the three chapters.

Student American Medical Association

The Chicago Medical School Chapter of the Student American Medical Association recently inaugurated its program of lectures and motion pictures with an interesting address by Dr. Leon H. Strong, entitled "The History of Anatomy." Future lectures and pictures have already been scheduled.

In the chapters first elections, Seymour Kuvin was elected President; Norman Bacher, Vice-President; Julius Buchwald, secretary; and Solomon Chazan, Treasurer. Dr. A. H. Ryan has been appointed faculty advisor.

This chapter as a charter member of the S.A.M.A. is at present engaged in the fostering of chapter formation at other medical schools throughout the country. Chapters are already functioning at many other medical schools both in Chicago and in other states. With increased membership throughout its chapters, S.A.M.A. hopes to become the organization representing the majority of med-

ical students and aims to aid in bringing the student closer to the medical profession, both in its interests and affairs.

* * * *

COOK COUNTY HOSPITAL OUTLINE FORM

The following outline is the official guide used in the Cook County Hospital for its internes and residents to systematize their description and discussion of a particular disease process. We believe that the medical student and practicing physician will also find this guide of value in their studies and practices.

I. DEFINITION: This should include briefly the causative factor and the chief pathological and clinical features of the disease.

II. ETIOLOGY: Give a brief opening statement.

A. Predisposing Factors. Name them in the order of their importance. This will vary with the individual diseases.
   1. Endemic, epidemic or sporadic
   2. Heredity
   3. Sex
   4. Age, including congenital
   5. Race
   6. Climate and season
   7. Geography
   8. Individual predisposition.
      a. Alcohol
      b. Other habits
      c. Previous or coexisting diseases
      d. Social condition
   9. Hygiene
      a. Water
      b. Food
      c. Sanitation
      d. Insects
   10. Occupation
   11. Exposure to other causes and cases

B. Exciting Causes:
   1. Essential organism, parasite, or bacterium, or theories as to cause.
   2. Morphology: size, shape, spores, motility, and staining reactions (as with the Gram and special stains).
   3. Cultural Characteristics: anerobic or aerobic, media, optimum temp., gas production, durability, and agglutination reactions.
   4. Distribution: In the body, outside of the body.
   6. Immunity.
   7. Associated bacteriology, if any.

III. PATHOLOGY.

A. General opening statement

B. Pathogenesis

C. Essential Changes
   1. Gross: size and weight, position, surface, shape, consistency, number of lesions and capsular changes.
   2. Cut Sections: consistency, moisture, edema, hyperemia, markings and color.
   3. Microscopic: essential changes in parenchyma, interstitial changes, blood vessels, lymphatics & nerves.

D. Complications: Name chief ones and describe briefly.

E. Associated Pathology: including rarer findings and listing symptoms. Circulatory, pulmonary, gastro-intestinal, nervous, genito-urinary, special senses, skin, glands, lymphatics, hematopoetic organs, bones, joints, and musculature.

IV. SYMPTOMATOLOGY.

A. General Opening Statement

B. Incubation

C. Prodromes

D. Symptoms in typical cases
   1. Onset
   2. Subjective complaints, such as pain, cough, etc.
   3. Objective findings
      a. General findings: Temp., pulse, respirations, BP, and skin. A rash should be described according to the time of onset, the location, the character, the duration and the type of desquamation if any.
      b. Local findings: by inspection, palpation, percussion, and by auscultation.
      c. Laboratory findings: including X-Ray.
   4. Course: stages (duration and symptoms of each), duration, termination by lysis or crisis, and convalescence.

E. Varieties or Types.

F. Complications and Sequelae.

V. DIAGNOSIS.

A. Direct: based on the history of an epidemic, etc., finding the etiologic factor, cardinal symptoms, physical findings, laboratory findings, and course.

B. Differential: Opening statement, chief points of any disease which may be confused with the one being discussed.

VI. PROGNOSIS. Average mortality, favorable factors, unfavorable factors, and cause of death.

VII. TREATMENT.

A. Prophylactic.
   1. Individual.
   2. General measures: Vaccines, sera, medicines, etc.
   3. General health measures, isolation of patient when exposed, sanitation of community, etc.

B. Active:
   1. Specific: local and general.
   2. Symptomatic. Local and general.
   3. General measures: hygienic, diatetic, eliminative, medical, hydrotherapeutic, mechanotherapeutic, etc.
   4. Surgical, indications and contraindications, conditions.
   5. Convalescent.

NEW BOOKS IN THE LIBRARY

Allee, W. C., et al. Animal ecology. 1949.
Am. As. Anat. 61st annual meeting. Abstracts. 1948.
Ann. review of microbiology. Vol 2, 1948.
Ann. review of physiology. Vol. 11, 1949.
Ashford, M., ed. Trends in medical education. 1949.
Babkin, B. P. Secretory mechanism of digestive glands. 2nd ed. c1950.
Brackett, G. S. Coccidiosis. 1949. (Ann. N. Y. Acad. Sci., *52*, 4).
Bradley, O. C. Anatomy of dog. 5th ed. 1948.
Flynn, J. E., ed. Blood clotting and allied problems. 1949.
Goepp & Flippin. Med. state board questions and answers. 8th ed. 1950.
Hall, M. F. Public health statistics. 2d ed. rev. c1949.
Harrison, B. M. Embryology of chick and pig. c1949.
Internat. Poliomyelitis Congress. Poliomyelitis. c1949.
Library of Congress. Communism in action. 1946.
Mason, E. E. Vitamin E. 1949. (Ann. N. Y. Acad. Sci., *52*, 3).
Massey, A., ed. Trends in public health. 1949.
Mountain, J. W. Health service areas . . . physician requirements. 1949.
Public Health Inst. How laymen cut medical costs. c1948.
Rockefeller Inst. Medical Research. Studies. v. 139. 1949.
Rolnick, H. C. Urology. 2 vols. c1949.
Schoenewald, F. S., comp. German-English med. dictionary. 1949.
U. S. Bureau of Census. Vital Statistics. 1947. 1949.
U. S. Office of Education. Statistics of libraries in institutions of higher education. 1949.
U. S. Pub. Health Service. Serologic tests for syphilis. 1949. 2d cop.
Vitamins and Hormones. Vol. 7. 1949.
Wells, B. B. Clinical pathology. 1949.
Wever, E. G. Hearing. c1949.
Wolff & Wolf. Pain. (1349.)
Yagoda, H. Radioactive measurements with nuclear emulsions. 1949.
Yearbook of surgery. 1949.
Yearbook of obstetrics and gynecology. 1949.

Bailey, H. Physical signs in clinical surgery. 11th ed. 1949.
Cattell, J. McK., ed. American men of science. 8th ed. 1949.
Coca, A. F. Allergy. 1949 (Ann. N. Y. Acad. Sci., *50*, No. 7,679-814).
Cole, W. H., ed. Operative technique in general surgery. c1949. 2 vols.
Cowdry, E. V. Laboratory technique in biology and medicine. 2d ed. 1948.
Davis, H. A. Shock. 1949.
Grulee & Eley. Child in health and disease. 1948.
Hamilton, A. Industrial toxicology. 2d ed. rev. c1949.
Harrison, B. M. Embryology of chick and pig. c1949.
Hebb, D. O. Organization of behavior. 1949.
Kreider, P. G. Bacteriology, pathology and etiology of measles pneumonia. c1943.
Hamman, L., et. al. Acute diffuse interstitial fibrosis of lungs. 1943. (Mellon lecture.)
Mack, P. B. & Urbach. Study of institutional children. 1949. 2 cop.
Mollison, P. L., et. al. Rh blood group. 1948.
Parker, V. Index to current period literature on neoplastic diseases. 1949.
Pick, J. F. Surgery of repair. c1949. 2 vols.
Rake, G. W. Chemotherapy of tuberculosis. 1949. (Ann. N. Y. Acad. Sci., *52*, No. 5, 625-788.)
Skiner, H. A. Origin of medical terms. 1949.
U. S. Index-catalog of medicine and veterinary zoology, pt. 11. 1950.
U. S. Postal Dept. Official postal guide. 2 parts. 1949.
Voegtlin, C. & Hodge, H. C., eds. Pharmacology and toxicology of uranium compounds. 1949. 2 vols.
Yearbook of eye, ear, nose and throat. 1949.

ADDITIONS TO THE OPPENHEIM COLLECTION FROM HIS LIBRARY

Brown, A. M. Modern plastic surgical prosthetics. 1947.
Directory of medical specialists. Vol. 4. 1949.
Gans, Oskar. Histologie der Hautkrankheiten. 1925-28. 2 vols.
International who's who in world medicine. 1947.
International world who's who (1948-49). c1949.
Kagan, S. R. The modern medical world. 1945.
Massengill, S. E. Sketch of medicine and pharmacy. (c1943.)
Mayo Clinic. Collected papers. Vol. 34, 1942.
Oppenheim, M. Reprints. Various dates.
Simon, C. Dermatologie, clinique et therapeutique. 1946.
World biography, c1948. 2 vols.

NEW JOURNALS

Electroencephalography, vol. 1, 1949.
Industrial hygiene newsletter, vol. 9, 1949.
Mexico. Univ. nacional. Institute de Biologia. Anales. Vol. 20, 1949.
Revista Argentina de Cardiologia, vol. 16, 1949. (Gift of Doctor Luisada.)

M. E. Campbell, *Librarian*